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1210 MEDICO-DENTAL BUILDING
SAN DIEGO, CALIFORNIA

ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

Hospital Library

VOL. 13 (O.S., Vol. XVIII) AUGUST, 1939 NUMBER 2

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Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $7.50, other countries.

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ANNALS OF
INTERNAL MEDICINE

VOLUME 13 AUGUST, 1939 NUMBER 2

NICOTINIC ACID IN NUTRITION *

By C. A. ELVEHJEM, *Madison, Wisconsin*

IT is the goal of nutrition workers to make available as rapidly as possible all the knowledge necessary to handle the supply of foods and the demand for nutrients in such a way that nutritional deficiencies will be reduced to a minimum. However, there are many factors such as habit, economic conditions, ignorance, commercial manipulation of food supplies, etc., which militate against the attainment of this goal.

When nutritional deficiencies appear, the physician is expected to bring about rapid recovery even though the condition is the result of prolonged consumption of inadequate diets. It is apparent to most of us that the number of nutritional disorders is not decreasing. There are undoubtedly two reasons for this situation. First, more and more diseases are being associated with nutritional disturbances; and secondly, in spite of our increased knowledge of nutrition, the American diet is still far from ideal.

There is ample evidence that the knowledge necessary for the treatment of nutritional diseases has come from direct observations in the field and from experimental studies with laboratory animals. In fact many diseases were not conquered until the experimental animal entered the picture. There are, of course, exceptions, such as pernicious anemia, but this does not mean that greater progress might not have been enjoyed if it were possible to produce a similar disease in animals. During the past one and one-half years we have seen the fairly successful use of nicotinic acid in the treatment of pellagra and certain related disorders. I imagine my appearance on this program is dependent upon the fact that the discovery of the nutritional significance of nicotinic acid happened to be made in my laboratory. I do not mean to infer that we did not make a concerted effort to isolate the antipellagra factor, but I do want to emphasize that evidence for the significance of nicotinic acid in metabolism was accumulating in many laboratories.

* Given before the New Orleans meeting of the American College of Physicians, March 29, 1939.

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Therefore, I do not propose to talk as an authority on pellagra or on the use of nicotinic acid in human nutrition. However, a survey of the work which led to the recognition of nicotinic acid may bring out certain helpful suggestions in the treatment of pellagra, as well as other nutritional diseases. Let us consider the status of pellagra and the antipellagra factor in 1930. The excellent work of Goldberger and coworkers had established pellagra as a deficiency disease. The protective factor was associated with the more heat stable fraction of the B complex which had been distinguished from vitamin B_1 by animal experimentation. A pellagra-like condition had been produced in rats on diets low in the B complex supplemented with an alcoholic extract of corn. Considerable difficulty was encountered in producing this condition consistently, but the growth stimulating effect of various foods when added to this diet continued to be used as a measure of antipellagra activity. In fact all the values in the literature were based on these assays except the limited figures reported by Sebrell [1] from studies with dogs. As late as 1932 Harris [2] made the following statement in a review on the water soluble vitamins. "The available evidence fairly well supports the assumption that the B_2 vitamin, as measured by the rat growth technic corresponds essentially with the pellagra-preventive factor for humans. Many aspects of the question, however, are still in the arena of controversy."

In 1930 the value of liver extract in the treatment of pellagra in man as well as its activity in the prevention of vitamin B_2 deficiency in rats was recognized. Goldberger and Sebrell [3] found liver extract 343 to be a good source of the factor necessary for the prevention of black tongue in dogs. Spies [4] and Smith and Ruffin [5] found that fairly large amounts of liver extract by mouth were efficacious in treating pellagra. At about the same time I was working in the Biochemical Laboratory, Cambridge, England, and Dr. Guha, who was also working there, found that the liver extract, which I had brought along for another purpose, produced excellent growth in rats on a vitamin B_2 deficient diet. The following year Salmon and Guerrant [6] found liver extract to be four times as rich in vitamin G (B_2) as a sample of brewer's yeast. We now know that the growth obtained in both cases must have been due mainly to the riboflavin present in the liver extract. However, the above results were sufficient to convince me that liver extract might be an excellent material for the isolation of the antipellagra factor.

Attempts in our laboratory to produce pellagra-like lesions in rats failed completely, and we turned our attention to chicks. A pellagra-like condition was produced in the chick by feeding a heated natural grain ration, and the assays of our fractions from liver extract depended upon the prevention of these lesions. We [7] soon had the first indication that the factor active in this syndrome was separate from riboflavin which Kuhn, György, and Wagner-Jauregg [8] had just isolated and shown to have growth-promoting properties in rats. Concentrates of flavin were completely inactive for the chick whereas purified fractions from liver retained their potency after complete removal of riboflavin. Lepkovsky and Jukes [9] soon confirmed our

experimental results and introduced the name " filtrate factor " for the active substance in the filtrate after removal of the flavin with fuller's earth. This designation did not exactly please us since naturally we felt that we were dealing with the antipellagra factor, and Dr. Lepkovsky and I had many friendly arguments over the question. We both recognized that there was no evidence available to show that the pellagra-like condition in chicks was identical with human pellagra. It was therefore necessary for us to repeat our work using dogs, since most authorities agreed that black tongue in dogs is identical with human pellagra. Again [10] flavin had no effect on black tongue whereas the purified concentrates free of flavin were highly active in curing black tongue. Birch, György and Harris [11] soon confirmed the fact that flavin had no curative action in dogs, and Dann,[12] Spies,[13] and Fouts, Lepkovsky, Helmer, and Jukes [14] reported complete inactivity of flavin in the treatment of human pellagra.

Further purification of the liver fractions gave concentrates which contained very small amounts of solid material and which were highly active in both chicks and dogs. We were inclined to believe that the chick and dog required the same factor. Within a very short period we [15] demonstrated the activity of nicotinic acid in the cure of black tongue, and isolated nicotinic acid amide from the liver extract concentrates. When we [16] tried nicotinic acid or the amide on the chicks they were completely inactive. Thus the chicks had provided an excellent means of assay, not because we were actually testing for nicotinic acid, but because we were testing for the chick antidermatitis factor which followed nicotinic acid amide very closely.

I hope I have not bored you with these details, but they demonstrate the importance of using different species when studying human nutrition. I do not mean to infer that the fundamental metabolism in different species varies greatly, but it is evident that we may be more successful in producing certain deficiencies in one animal and other deficiencies in another species. Thus the rat was used successfully in separating the antipellagra factor from vitamin B_1, the chick for separating it from riboflavin, and the dog for establishing its relation to nicotinic acid and not to the chick antidermatitis factor. In fact at the present time no one has been able to demonstrate that either the rat or the chick needs nicotinic acid preformed in the diet—yet cozymase, which contains nicotinic acid, is present in both rats and chicks.

Returning to the rat, this animal has been valuable in demonstrating the existence of at least two additional factors in the B complex; namely, vitamin B_6 and factor W. In the absence of vitamin B_6 the rat develops acrodynia, which is undoubtedly the same condition which was called pellagra in the earlier work. Birch, György, and Harris [11] in 1935 demonstrated conclusively that vitamin B_6 was distinct from the antipellagra factor. They found corn and molasses, foods known to be deficient in the P–P factor, to be good sources of vitamin B_6 and liver extract, which was rich in the P–P factor, to be low in vitamin B_6. Today if we give nicotinic acid to rats suffering from vitamin B_6 deficiency, there is no improvement whatsoever.

Very recently Helmer, Fouts, Lepkovsky, and Jukes have produced a hypochromic anemia in dogs on a vitamin B_6 low diet and have cured the condition with crystalline vitamin B_6.

If rats are placed on a purified diet devoid of all the B vitamins, and if thiamine, riboflavin, nicotinic acid, vitamin B_6, and chick antidermatitis factor are supplied in adequate amounts, the rats fail to grow until another factor which we [17] have designated as factor W is added. We have recently obtained similar results with dogs. Factor W is present in the so-called filtrate from liver extract in addition to nicotinic acid and chick antidermatitis factor. Thus we have six separate and distinct B vitamins, and if I had time I could give you preliminary evidence for several more.

What does this mean in practical nutrition? Some of you may think that we are having a contest to see how many separate factors can be found. We will enjoy real success in the treatment of nutritional deficiencies only when all these factors are recognized. The real value of this knowledge will not depend so much on the use of the individual chemical entities, although this may be important in many cases, but rather on the interrelationship of each of these factors. Thus diets low in nicotinic acid or compounds which yield nicotinic acid on ingestion allow the development of pellagra, but such diets may also be low in other related vitamins. A diet deficient in only one nutritional factor but complete in all others is the ideal experimental diet which nutritional workers are continually looking for—but such rations are rarely obtained. Even those based on the original Goldberger diet contain some nicotinic acid and may be low in thiamine and riboflavin. The great value of the Goldberger diet is that black tongue develops before the other deficiencies are encountered, but now that we can add pure nicotinic acid, it is possible to demonstrate some of the other limitations. The supplementary value of thiamine and riboflavin in the treatment of pellagra has already been reported. Sebrell and Butler [18] have recently reported the development of riboflavin deficiency in patients maintained on the Goldberger diet. There may be other factors which are supplied in a limiting amount. Langston, Darby, Shukers, and Day [19] have obtained a nutritional cytopenia in monkeys maintained on the Goldberger ration. This syndrome was not cured by thiamine, riboflavin, or nicotinic acid, but liver extract contained the active factor. The Goldberger diet contains 65 to 75 per cent of corn. If this corn is replaced by sucrose and the required amounts of nicotinic acid, thiamine and riboflavin added, the dogs will grow for only a week or two and then begin to lose weight. The addition of 2 per cent liver extract renders the diet complete. Thus a small amount of liver extract supplies the same factors as 70 per cent of corn. Vitamin B_6 and factor W are at least two of the factors concerned here. Thus the results obtained with nicotinic acid may depend upon the actual amount of corn consumed by the patient.

It is evident therefore that there is danger in the wholesale treatment of pellagrins on severely deficient diets with pure nicotinic acid or purified

concentrates of nicotinic acid. What approach are we to make? First let me point out that foods carrying only fair amounts of nicotinic acid may be useless in treating severe pellagra regardless of the other factors they carry. Nicotinic acid is the critical deficiency and it must be provided before any response can be obtained. The great difficulties encountered in treating pellagra before nicotinic acid was available substantiate this conclusion. Similar evidence is available from our dog work. You will remember that Sebrell assayed foods for the P–P factor by determining what level of food would protect the dog from black tongue over a considerable period of time. We started with young dogs, produced black tongue, and cured the symptoms with concentrates and finally nicotinic acid. The response was very rapid. During the past year we have been assaying foods in the same way. When wheat germ, powdered milk, or dried grass is given in one dose, no improvement is obtained. The animal is unable to digest the food sufficiently to liberate the nicotinic acid present. Foods that are richer and can be fed in smaller quantities, such as liver, kidney, lean meat and yeast, work considerably better.

The rapid assimilation of nicotinic acid, even in the presence of severe intestinal disturbances, undoubtedly explains the success with which it has been used in the field. At present there appears to be no compound which is more useful. We [20] have tested a number of pyridine derivatives on dogs, and although nicotinamide, ethyl nicotinate, nicotinic acid N methyl amide, nicotinic acid N diethyl amide (coramin), and nicotinuric acid are active, none of these compounds seem to have any virtue over nicotinic acid. Trigonellin, pyridine, quinolinic acid, picolinic acid, isonicotinic acid, nipecotic acid, β-amino pyridine and related compounds are all inactive.

As long as severe pellagra is encountered, I imagine the use of nicotinic acid will have to be continued, but when it is used, we must remember that there are at least five other members of the B complex which may also be low. Fortunately both thiamine and riboflavin are available in synthetic form, and we are hopeful that some of the others may be available within a reasonable length of time. However, the supply of most of these factors through foods will be considerably cheaper for some time.

I cannot go into the great variations in the amount of nicotinic acid required for the treatment of pellagra in different patients. This has been discussed by Spies, Sydenstricker, and others. Several workers have observed considerable variation in the response made by different dogs to nicotinic acid. We have preliminary evidence that a more rapid response is obtained after feeding a factor W concentrate for a short time before giving nicotinic acid. Much more work is necessary, but these relationships are not surprising since at least four of the vitamins which I have discussed are related to the respiratory enzyme systems. Thiamine is related to cocarboxylase, which is necessary for the normal metabolism of pyruvic acid. Riboflavin is a component of flavoproteins, which act as hydrogen carriers, and probably also a component of the prosthetic group in other enzymes,

such as xanthine oxidase. Nicotinic acid is a component of both cozymase and cozymase II, both of which are coenzymes for a large number of oxidation mechanisms. We have recently shown that tissues taken from animals suffering from a factor W deficiency have a reduced rate of oxygen uptake.

I might mention our studies on the changes in the cozymase content of tissues during nicotinic acid deficiency. We used the Euler-Myrbäck method for estimating the cozymase content. Using both dogs and pigs we were unable to demonstrate any change in the blood, but very significant decreases were obtained in the liver and muscle during nicotinic acid deficiency.

Returning to the nutritional significance of nicotinic acid, I want to emphasize that the incidence of pellagra in certain areas of this country and other parts of the world is a temporary condition brought about by environmental conditions. Nicotinic acid as such is an emergency measure. Our goal should be the modification of the diet so that the people in these areas would obtain sufficient nicotinic acid, as well as the other essentials, from foods. This does not mean that certain foods could not be fortified with nicotinic acid, when experimental work has shown the proper means of fortification. In any case, the great need is further knowledge of the distribution of these factors in foods. I know it is a long and tedious job and one which is not very fascinating, but it must be done, and I hope that you as physicians will lend your support to such studies. I believe that this country is still sufficiently agricultural to produce the foods adequate for a normal diet, so that we may consume pleasing foods rather than obtaining our vitamins from the drug store except in emergencies.

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OBSERVATIONS UPON THE EXPERIMENTAL USE OF SULFAPYRIDINE. I. THE RELATION OF STRAIN RESISTANCE TO THE CHEMOTHERAPEUTIC EFFECTS OF SULFAPYRIDINE IN EXPERIMENTAL PNEUMOCOCCAL INFECTIONS IN MICE *

By Perrin H. Long, M.D., and Eleanor A. Bliss, Sc.D.,
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In the *Lancet* of May 28, 1938, L. E. H. Whitby [1] reported that 2 (p-aminobenzenesulphonamido) pyridine (sulfapyridine) was "chemotherapeutically active in experimental infections in mice against pneumococci of types I, II, III, V, VII, VIII and especially against types I, VII and VIII." Whitby also stated in this paper that the drug appeared "to exert a definite action on the capsule of the pneumococcus." Within a very short time after this communication appeared, Evans and Gaisford [2] reported that they had treated with sulfapyridine 100 patients suffering from lobar pneumonia, and that in this group of patients the case fatality rate was 8 per cent; this was to be compared with a fatality rate of 27 per cent in a group of 100 patients who had received symptomatic treatment for lobar pneumonia. These important observations naturally created a great deal of interest throughout the world. It was not very long before general confirmation of Whitby's observations began to appear [3-9] and, while the results of certain investigators were at partial variance with those reported by Whitby, there can be little doubt that sulfapyridine is a fairly satisfactory agent for the treatment of experimental pneumococcal infections in mice. In this communication we will record certain of our observations upon the use of sulfapyridine in pneumococcal experimental infections.

During the past year we have conducted extensive experiments upon the chemotherapeutic properties of sulfapyridine in experimental pneumococcal infections in mice. The results of these observations are recorded in table 1. We soon noted that while sulfapyridine produced more satisfactory results in the treatment of pneumococcal infections in mice than we had obtained previously with any other chemical compound, nevertheless, we could not approach those reported by Whitby. This was especially true insofar as our results in the treatment of type I pneumococcal infections were concerned.

A review of our methods of inoculation and of our systems of dosage showed no great divergence from those used by Whitby.[1] We were at first

* Received for publication July 1, 1939.
This investigation was supported by a grant from The Chemical Foundation, Inc., of New York City.
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TABLE I

Sulfapyridine Therapy in Experimental Pneumococcal Peritonitis in Mice

No. Mice	Organism	Inoculum M.L.D.	Type of Treatment	Deaths—Days after Infection											Survivals	
				1	2	3	4	5	6	7	8	9	10	11–30	No.	%
130	Pneu. I	950	D 10		15	47	39	15	1	2				1	10	7.7
40	Pneu. I	575	F 10		2	14	17	4					1	1	1	2.5
35	Pneu. I	805	G 20		23	11	1								0	0
20	Pneu. I	500	H 30		4	14	1	1							0	0
190	Pneu. I	775	Controls	188	2										0	0
50	Pneu. II	890	D 10		7	13	10	5	7	6	1	1			0	0
30	Pneu. II	890	Controls	30											0	0
50	Pneu. III	1040	D 10	1	4	6	8	2	1	25	2	1			0	0
30	Pneu. III	1040	Controls	30											0	.0

D 10 = 10 mg. *per os* T.I.D. for 5 days, B.I.D. for 1 day, Q.D. for 1 day.
F 10 = 10 mg. *per os* 4 I.D. for 4 days, T.I.D. for 2 days, B.I.D. for 2 days, Q.D. for 1 day.
G 20 = 20 mg. *per os* at 4 and 12 hours after infection, then Q.D. for 4 days.
H 30 = 30 mg. *per os* immediately after infection and 6 hours later, then Q.D. for 3 days.

inclined to attribute our less favorable results to a greater "virulence" of our strains of pneumococci for the mouse. However, after MacLean, Rogers and Fleming [10] reported that, upon the basis of their in vitro studies, they had reached the conclusion that pneumococci might vary markedly in their sensitivity to the drug and had apparently confirmed this by in vivo treatment tests, we began to wonder whether our highly "virulent" strain might not also be relatively insensitive to the chemotherapeutic effects of sulfapyridine.

We [8] had tested previously the bacteriostatic effects of sulfanilamide and sulfapyridine upon the growth of our type I strain of pneumococcus in beef infusion, neo-peptone dextrose broth, and had found the strain to be moderately sensitive to sultanilamide and quite sensitive to sulfapyridine. Retests of the bacteriostatic activity of these two compounds are shown in table 2. It is to be noted that under the conditions of the test, sulfapyridine was a highly effective bacteriostatic agent.

TABLE II

The Bacteriostatic Effects of Sulfapyridine and Sulfanilamide upon the Growth of Five Strains of Type I Pneumococci in Beef Infusion, Neo-Peptone Dextrose Broth Cultures

Organism	Inoculum orgs./c.c.	Growth—Colonies/1 c.c. in 18 hours		
		Control	Sulfanilamide 10 mg. %	Sulfapyridine 10 mg. %
I	600	150 mil.	1,120,000	100
	400	80 mil.	3,400	10
	1,450	100 mil.	141,000	2,000
S V–I	760	160 mil.	147,000	2,140
	22,000	130 mil.	46,000	330
	1,180	70 mil.	15,000	11,000
S V–I/P/47	1,180	90 mil.	32 mil.	480,000
	56,000	140 mil.	190 mil.	25 mil.
	1,400	100 mil.	110 mil.	147,000
	19,200	720 mil.	380 mil.	5 mil.
	720	510 mil.	300 mil.	125,000
	840	190 mil.	350 mil.	590,000
Neufeld I	480	240 mil.	35,000	500
	220	210 mil.	330	10
	2,400	160 mil.	12,000	19,000
Neufeld I	860	430 mil.	10,000	2,100
	660	290 mil.	7,000	1,060
	2,200	220 mil.	2,000	3,000

I = Highly mouse-virulent, in vivo sulfapyridine resistant strain.
S V–I = Highly mouse-virulent, in vivo sulfapyridine susceptible strain obtained from Dr. Colin MacLeod.
S V–I/P/47 = Highly mouse-virulent, in vivo sulfapyridine resistant strain obtained from Dr. Colin MacLeod.
Neufeld I = Originally came from the New York State Board of Health Laboratories.
Neufeld I = Originally came from the New York City Board of Health Laboratories.

TABLE III

The Comparative Therapeutic Effects of Sulfapyridine in Experimental Pneumococcal Infections in Mice Produced by "Resistant" and "Susceptible" Strains of Type I Pneumococci

No. Mice	Organism	Inoculum M.L.D.	Type of Treatment	Deaths—Days after Infection											Survivals	
				1	2	3	4	5	6	7	8	9	10	11–30	No.	%
20	Pneu. I	500	H 30		4	14	1	1							0	0
10	Pneu. I	500	Controls	10											0	0
20	Pneu. I (SV/1)	620	H 30	1		1			1						17	85
10	Pneu. I (SV/1)	620	Controls		10											
20	Pneu. I (SV/P47)	560	H 30	1	10	7			2						0	0
10	Pneu. I (SV/P47)	560	Controls		10											

H 30 = 30 mg. *per os* immediately after infection and 6 hours later, then Q.D. for 3 days.

At this point Dr. Colin MacLeod informed us that he had developed a "sulfapyridine-fast" mutant from a strain of type I pneumococcus, the original strain having been very susceptible to the chemotherapeutic effects of sulfapyridine. He very kindly sent us the parent strain S V–I and the "sulfapyridine-fast" strain S V–I/P/47, the properties of which he has recently described.[11, 12]

These strains, together with Neufeld type I strains from two different sources, were tested by our technic to determine their sensitivity to the bacteriostatic effects of sulfanilamide and sulfapyridine in vitro. As will be noted in table 2, the parent strain S V–I and the two Neufeld strains were as susceptible to the bacteriostatic effects of sulfapyridine as was our own type I pneumococcus. The "sulfapyridine-fast" organism S V–I/P/47 was, on the contrary, quite insensitive to the bacteriostatic effects of sulfanilamide and was only moderately sensitive to the effects of sulfapyridine. MacLeod[11] has shown that experimental infections in mice produced by the S V–I strain yield readily to treatment with sulfapyridine, and that the converse is true with infections produced by strain S V–I/P/47. We, therefore, tested the comparative therapeutic effects of sulfapyridine in infections produced in mice by inoculation of our type I strain of pneumococcus, S V–I and S V–I/P/47. The results of these therapeutic attempts are recorded in table 3.

As was to be expected from our previous experience, no mice infected with our strain of type I pneumococcus survived. The same was true of the mice infected with the "sulfapyridine-fast" strain S V–I/P/47, while 17 of the mice infected with strain S V–I survived. It is interesting to note at this point that the control mice infected with strains S V–I and S V–I/P/47 died on the second day of their infection, while the other control mice died within 22 hours after they were inoculated.

Discussion

These experiments confirm the observation, as has already been pointed out, that strain differences in the susceptibility of pneumococci to sulfapyridine do exist. Furthermore, they reveal the fact that strains of pneumococci which appear to be highly susceptible to the in vitro bacteriostatic effects of sulfapyridine may produce infections in vivo which differ markedly in their response to the chemotherapeutic action of the drug. They also serve to emphasize again the possibility that naturally resistant strains exist and that the mechanism of this resistance to the chemotherapeutic effects of sulfapyridine in vivo may be quite different from that of a normally susceptible strain. Certainly, the variations in the response of the organisms to the in vitro bacteriostatic effects of sulfapyridine suggest that this might be true. The practical significance of these observations lies in the fact that it has been shown that marked strain differences in susceptibility do occur and, hence, it would be wise to take advantage of this fact in

assessing the activities of new chemical compounds. They also suggest that variations in the susceptibility of pneumococci to sulfapyridine will be of importance in the therapy of pneumococcal pneumonia in man with the drug.

Conclusion

Marked differences exist among strains of pneumococci in their response to the chemotherapeutic effects of sulfapyridine.

We are indebted to the Calco Chemical Company, Inc., and to Merck and Company, Inc., for the sulfapyridine used in these experiments.

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EPIDEMIC SYPHILIS, ITS RECOGNITION AND MANAGEMENT BY THE PHYSICIAN*

By E. GURNEY CLARK, M.D., *Nashville, Tennessee*

INTRODUCTION

SYPHILIS exhibits many of the characteristics of epidemic disease. It has the capacity of producing a sharp increase in incidence in a short time.[1] It often gives rise to localized outbreaks; and, in at least one historic instance, it appeared as a sudden outbreak over a wide area. This concept with regard to syphilis is not a new one. More than 100 reports of localized epidemics of syphilis can be found in the literature under titles which imply epidemicity.

The mild character or total absence of the early manifestations; the "conspiracy of silence" with regard to the disease; and the almost universal failure to recognize its epidemic nature are the factors that prevent its ultimate eradication or control. The recognition and management of epidemic syphilis are obligations of the medical profession.

EPIDEMICS OF SYPHILIS

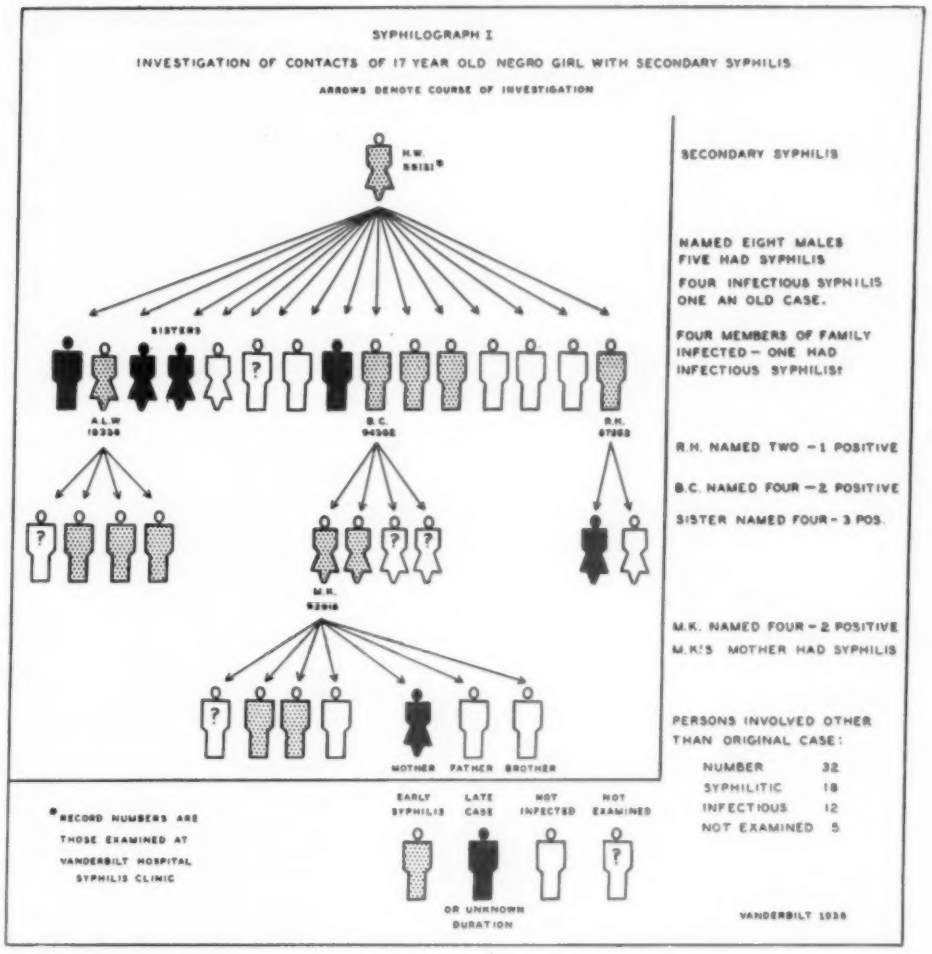
The following epidemics were discovered and brought under control in the routine management of patients in the syphilis clinic of the Vanderbilt University Hospital.

A young negro girl, H. W. (syphilograph 1), came to the clinic because of early syphilis of the skin and mucous membranes. When she learned that the lesions were due to syphilis and were highly infectious and that she had doubtless exposed others to the disease she disclosed the names of eight young men with whom she had had sexual intercourse and promised to assist in persuading them to have an examination. All of these and six members of her family were examined either by their own physicians or in the syphilis clinic of the Vanderbilt University Hospital. Of these 14 persons, nine were found to have syphilis, five of whom were in an infectious stage. A sister, A. L. W., was totally unaware of her infectious lesions and because of this it was a simple matter to develop in her a sympathy for her contacts who might have no knowledge of lesions. She designated four sexual contacts, three of whom were found by their own physicians to have infectious or potentially infectious syphilis. If these physicians investigated the contacts of these young boys it was not brought to our attention. B. C. and R. H., two of the sexual contacts of the original case, were examined by us and found to have secondary syphilis. Two others were also infectious. Three of the contacts were not infected. One was found to have inadequately treated syphilis of several years' duration. This patient was induced to return to his physician for continuance of his treatment. Subsequent examination of other contacts related to this epidemic disclosed four additional cases of early syphilis and

* Read at the New Orleans meeting of the American College of Physicians, March 29, 1939.

From the Department of Medicine, Vanderbilt University School of Medicine.

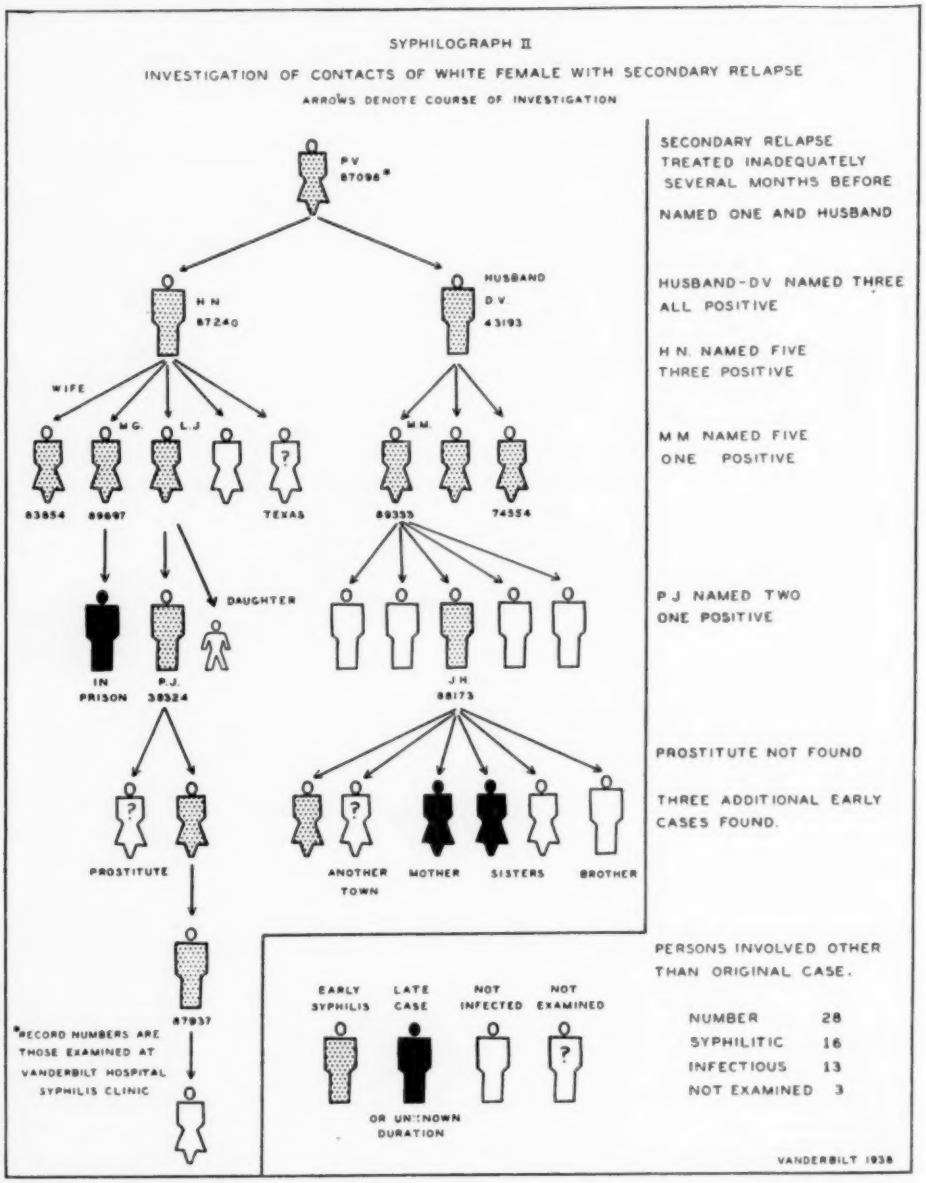
The epidemiological investigations were made possible through funds granted by the United States Public Health Service.



was instrumental in returning two old cases to treatment. In this epidemic 18 cases of syphilis were found among 32 persons designated as contacts. Several were totally unaware of the fact that they had syphilis or that they had been exposed to it.

A married white woman, P. V. (syphilograph 2), sought treatment because of a recurrence of a generalized rash six months after inadequate treatment for syphilis. A frank discussion convinced her of the danger of lapsing treatment and induced her to name one extra-marital contact. Her husband, also exhibiting secondary lesions, disclosed three of his contacts, all of whom were found to have infectious syphilis. One of these, M. M., brought to the clinic one of her contacts, J. H., who had primary syphilis, and named three others who were found not to be infected. H. N., the designated extra-marital contact of P. V., disclosed five names and three of the girls had early syphilis. Three additional cases were disclosed. Sixteen of the 26 persons involved were found to have syphilis. There were 13 of these who were infectious or potentially infectious.

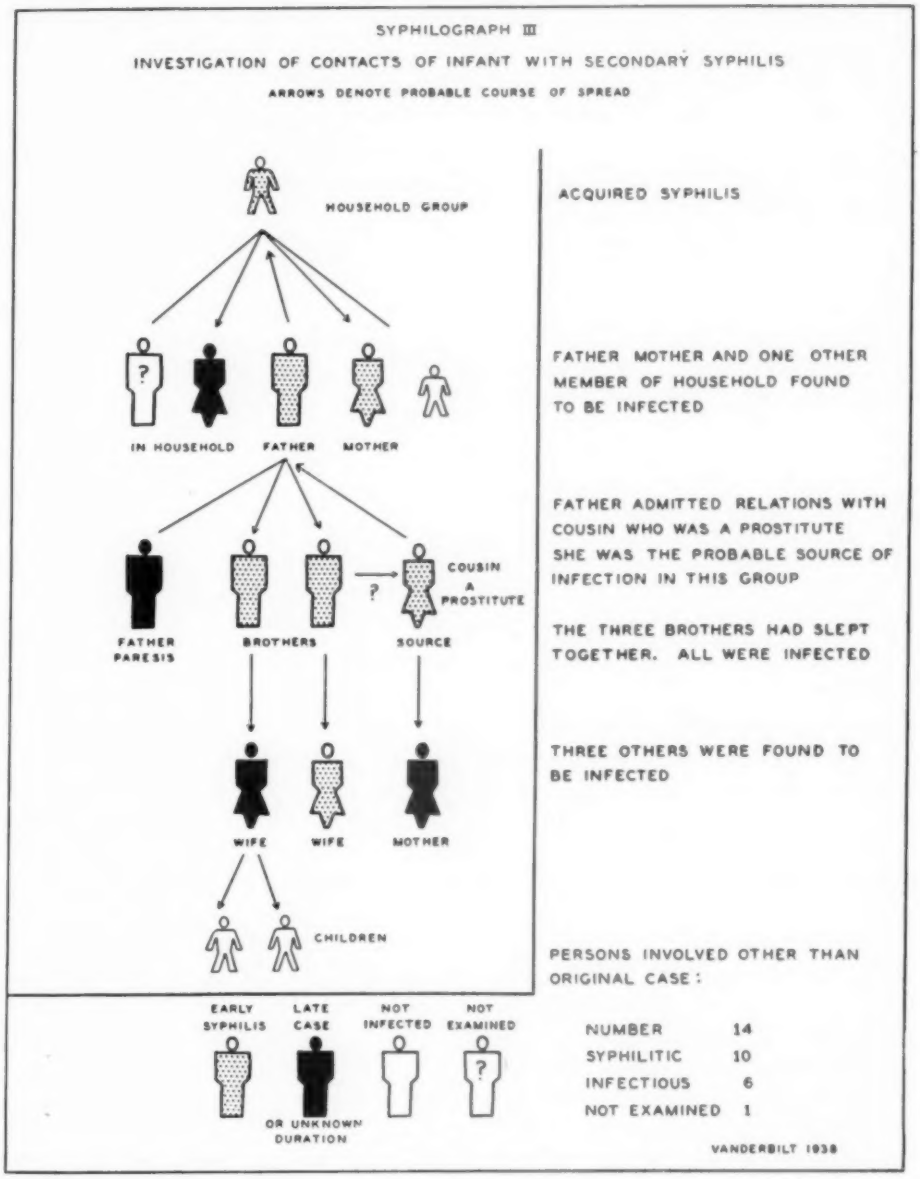
An epidemic of syphilis in a family is shown in syphilograph 3. Acquired syphilis was diagnosed in an infant seen in the pediatric clinic of the Vanderbilt University Hospital. The father, mother, two uncles and their wives, a cousin, a grandfather



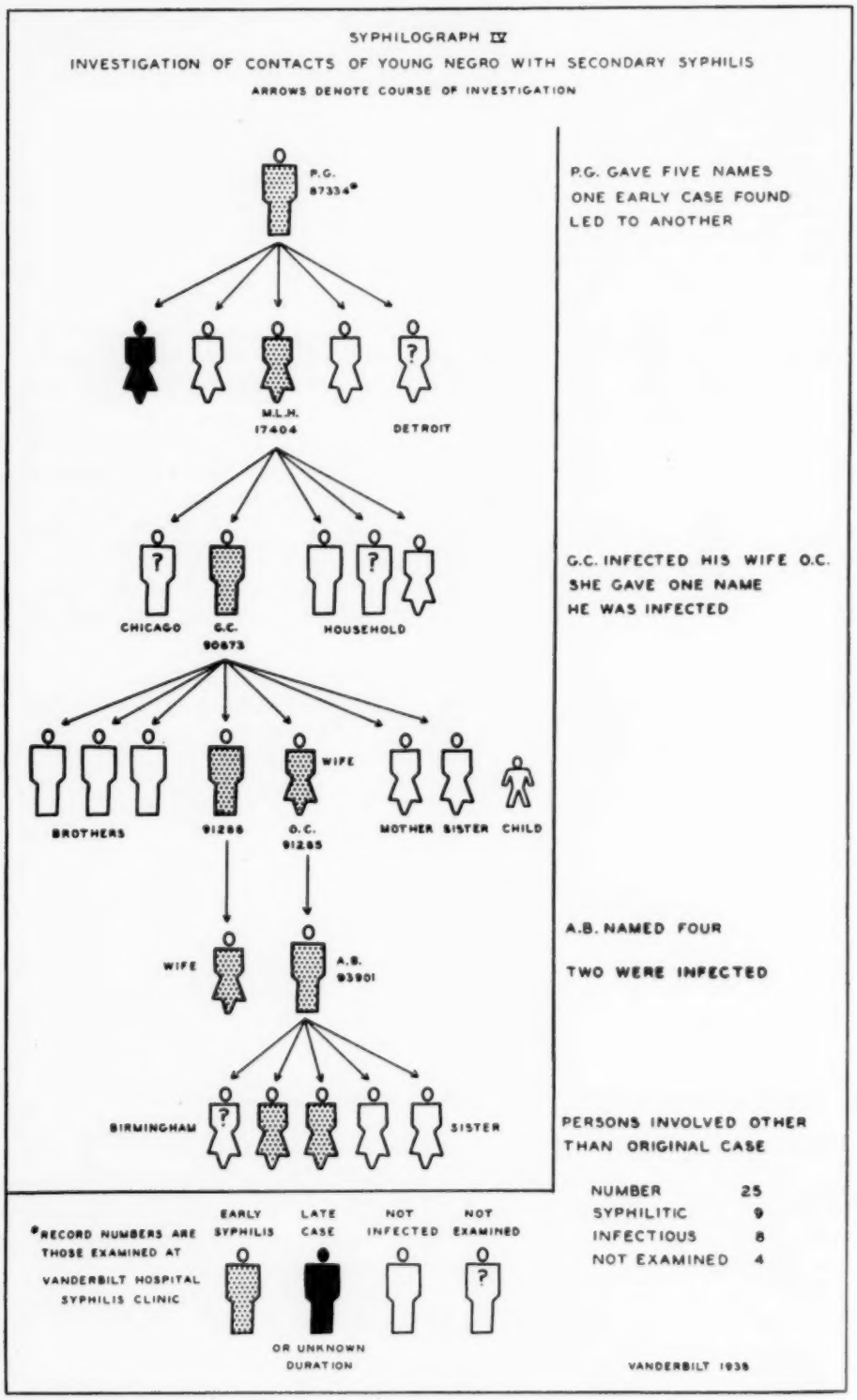
and another member of the household were found to have the disease. The source of the infection was thought to be a cousin who is a prostitute.

P. G., a young negro boy (syphilograph 4), was convinced by us that his name would not be divulged and gave information that led to the discovery of nine additional cases of syphilis.

These studies indicate that every case of syphilis is part of a localized outbreak; that the patient who comes to the physician can and often will



disclose facts which lead to the detection of this local epidemic. From this starting point the physician is able to discover and bring under control a large number of highly infectious individuals. The above four patients who sought treatment for acute syphilis were used as starting points and 39 additional infectious cases were disclosed.


SYPHILOGRAPH IV
INVESTIGATION OF CONTACTS OF YOUNG NEGRO WITH SECONDARY SYPHILIS
ARROWS DENOTE COURSE OF INVESTIGATION
P.G. 87334*
M.L.H. 17404
DETROIT
CHICAGO
G.C. 90873
HOUSEHOLD
BROTHERS
91286
WIFE
O.C. 91285
MOTHER
SISTER
CHILD
WIFE
A.B. 93901
BIRMINGHAM
SISTER
P.G. GAVE FIVE NAMES
ONE EARLY CASE FOUND
LED TO ANOTHER
G.C. INFECTED HIS WIFE O.C.
SHE GAVE ONE NAME
HE WAS INFECTED
A.B. NAMED FOUR
TWO WERE INFECTED
PERSONS INVOLVED OTHER THAN ORIGINAL CASE
NUMBER 25
SYPHILITIC 9
INFECTIOUS 8
NOT EXAMINED 4
*RECORD NUMBERS ARE THOSE EXAMINED AT VANDERBILT HOSPITAL SYPHILIS CLINIC
EARLY SYPHILIS
LATE CASE
NOT INFECTED
NOT EXAMINED
OR UNKNOWN DURATION
VANDERBILT 1938

Recognition of Epidemics of Syphilis by the Physician

The recognition of the epidemic is contingent upon the recognition of early syphilis in an individual. A high level of suspicion and the judicious use of all available diagnostic measures determine not only the difference between possible cure and ultimate disaster, but also, the difference between the control of infectiousness and the infection of others. Every subsequent infection may be the direct responsibility of the physician unless failure to make a diagnosis and to control the patient is unavoidable.

The diagnosis and treatment of the infected person does not terminate the physician's responsibility. The person who seeks medical advice may have been infected by a person devoid of knowledge of syphilis. The patient, in turn, may have unwittingly exposed many others before coming to the physician. As in other epidemic diseases, related cases are frequently found in the families of the infected persons as well as among sexual intimates. The patient, through conversation with his physician, can be convinced of his good fortune in obtaining an early diagnosis and a promise of cure. He can by virtue of his ignorance be freed of the blame of exposing others to the disease. In a short time there may be developed in him a sympathy for others whom he may have exposed or for the one who may have infected him. Candid, sympathetic and informative presentation of the problem to the patient enlists his assistance in bringing in for examination sexual partners and exposed members of his family or at least in a disclosure of names of contacts and a request that the physician assist in giving these the benefit of early diagnosis and treatment.

Theoretically, the incidence of syphilis should be much greater in this group of exposed individuals than in the general population. A study of the results of epidemiological investigation of patients seen in the syphilis clinic of the Vanderbilt University Hospital indicates that this is actually the case (table 1).[2]

Table I

Contacts of 242 Cases of Early Syphilis Seen at the Vanderbilt University Syphilis Clinic September 1, 1937 to August 31, 1938

	Number		Examined		Positive		Early Syphilis Found	
	Named	Accessible	No.	%	No.	% of Exam.	No.	% of Contacts Exam.
Family Contacts	783	719	565	78.7	155	27.4	98	17.3
Sexual Contacts	294	246	210	85.4	154	73.3	139	66.1
Total	1077	965	775	79.2	309	39.8	237	30.6

During a period of twelve months 242 patients with early syphilis were seen in the syphilis clinic. These individuals disclosed the names of 246

accessible sexual contacts. Of these, 210 (85.4 per cent) were examined and 139 (66.1 per cent) were found to have early syphilis. The examination of 565 (78.7 per cent) of the 719 accessible family contacts of these same patients revealed 155 (27.4 per cent) cases of syphilis of whom 98 had the disease in an early stage. Thus, by the application of epidemiological methods to the 242 cases of early syphilis 237 additional cases were found. Only 36 of these had previously consulted a physician. All were placed promptly under anti-syphilitic treatment.

It is of interest that only 4 (1.6 per cent) of the patients refused to coöperate and only 11 (4.5 per cent) claimed that their exposure had taken place in a house of prostitution. Twelve others claimed lack of knowledge concerning the names of sexual contacts.

There were 139 cases of early syphilis found among the contacts of 144 patients who were able to remember names of sexual partners.

Forty-nine cases of early syphilis were found among spouses of 83 married patients. Of the total marital partners examined 66.2 per cent were proved to have early syphilis (table 2). This is the same percentage

TABLE II

Results of Examinations of Spouses of Patients with Early Syphilis

Number of spouses	Examined		Positive		Found to Have Early Syphilis	
	No.	%	No.	%	Number	% of those examined
83	74	89.2	52	70.3	49	66.2

of early syphilis as among persons named as extra-marital sexual contacts (table 1).

MANAGEMENT OF EPIDEMIC SYPHILIS BY THE PHYSICIAN

The physician is more than a diagnostician and a therapeutist in the management of any disease. Attention has been directed to the rôle of the physician as a clinical epidemiologist by John R. Paul in his presidential address before the American Society for Clinical Investigation in 1938.[3] According to Paul the clinical epidemiologist " starts with a sick individual and cautiously branches out into the setting where that individual became sick—the home, the family, the workshop. He is anxious to search for other members of the patient's family or community group who are actually or potentially ill."

In no other disease is this more applicable than in syphilis. The management of epidemic syphilis depends upon the control of infectiousness not only in the known case but also in cases related to the known case. Success in the control of the known infection is directly proportional to the patient's understanding of his illness.[4] The informed patient coöperates in carrying

out treatment schedules; the confused or perplexed patient draws his own conclusions as to the time for cessation of treatment and usually the disappearance of signs and symptoms is his criterion of cure. This interpretation permits lapse from treatment long before the minimum requirements to control infectiousness have been satisfied. According to Stokes [5] 15 per cent of patients with early syphilis who receive less than 20 injections of an arsenical plus an appropriate amount of heavy metal will experience recurrence of infectious lesions. Thus, one of the most important factors in the control of infectiousness is the detailed explanation of the disease to the patient. This has been pointed out by Heller and Smith [6] and by Exner [7] and is indicated by our own studies of the effectiveness of patient education.[8]

The attendance records of 100 patients with early syphilis were studied. Fifty of these were seen in the clinic at a time when only casual instruction was given to each patient. The remaining 50 cases were told something about the nature of the disease, its outcome with and without treatment, and other factors intended to afford them a better understanding of their illness. This instruction was given by one individual and was about the same in all instances.

Table 3 shows the advantage of this instruction.

TABLE III

Attendance of Patients with Early Syphilis

	Casual Instruction		Detailed Instruction	
	No.	%	No.	%
Patients Studied	50		50	
Under Treatment 12 Months after Diagnosis	26	52	38	76
Those Receiving Minimum Treatment to Prevent Infectious Relapse (20 Arsenicals)	27	54	40	80
Average Visits, per Patient	27.6		37.4	

When detailed instruction was given, 80 per cent of the patients cooperated sufficiently to meet minimum treatment requirements. When casual instruction was given only 54 per cent met these requirements. The average number of visits of the former group was 37.4 (72 per cent attendance) and of the latter, 27.6 (52 per cent attendance).

Upon the physician rests the responsibility for the discovery of contact infections. The patient alone can identify his exposed contacts. The physician alone can identify the patient. The patient withholds the identity of exposed persons because he is ignorant of the potentialities of the disease. The physician, who is fully aware of these potentialities, should not be a

party to this " conspiracy of silence " and secrecy. He should not adhere to the obsolete notion that his obligation extends no further than his patient.

When the patient has been convinced of his responsibility to others, when he has been freed of blame for exposing others, and when he has been assured that his identity will not be revealed, he should be asked to divulge the names of his contacts during the time which includes the incubation period of the disease. In many instances the patient can be depended upon to bring these contacts to medical attention. In other instances a different approach must be made. In several localities methods similar to those provided for other infectious diseases have been used to assist the medical profession in bringing in for examination the contacts of patients with syphilis. Where such means are not available the local profession might be instrumental in developing them.

Nelson [9] in Massachusetts employed a trained case worker to do contact and follow-up work for physicians in private practice. This worker, although paid by the Department of Health, acted as an agent of the private physician in the investigation of contacts of his patients. No names were carried back to her office. At the time Nelson instituted this plan (1932) he was able to interest only six of 23 physicians in the venture. Eight of nine contacts whose names were given to the worker for investigation were brought under medical care in a short time. The possibilities of such a plan are apparent.

In New Jersey from 1926 to 1935,[10] 2,295 names of contacts of patients with venereal disease were furnished by physicians to the Bureau of Venereal Disease of the State Department of Health. Examinations were made in 57 per cent (1313) of these cases. Patients themselves were responsible for bringing to examination 268. The Health Department induced the remainder (1,023) to submit to an examination. Syphilis was diagnosed in 946 instances.

The advisability of repeated examinations of the contacts of patients with syphilis cannot be over-emphasized. Variations in the incubation period of early lesions, and in the time of appearance of sufficient reagin in the blood, make it imperative that reëxaminations be made for skin and mucous membrane lesions and that serologic tests be repeated at frequent intervals during the three month period following the last exposure to infection.

Summary and Conclusions

Syphilis is an epidemic disease. The recognition of this is one of the responsibilities of the physician. The management of the epidemic is in his hands. By means of education he may convince his patient of the need for continued treatment and thus prevent the spread of the disease from one reservoir of infection. The patient alone can identify the exposed contacts who may have become infected and who may be responsible for the further spread of the disease.

Successful methods have been formulated to investigate persons who have been designated as contacts. Where such methods have not been made available the physician may effectively assist in their development.

This is a new field for the clinician. It is one referred to by Paul [3]: "If these fields are eventually to be investigated, it is the man with clinical judgment who can best blaze the trail, for it is the prime responsibility of the clinician to do the work. It is his responsibility far more than that of the public health man, or the bacteriologist, or the chemist. To do this the clinician will, however, have to adopt a new technic and a new uniform."

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ANAPHYLAXIS AND ALLERGY *

By Carl A. Dragstedt, Ph.D., M.D., *Chicago, Illinois*

Probably the first definite suggestion that clinical allergy is related to experimental anaphylaxis was made by Wolff-Eisner [1] in 1905. Since that time numerous workers have noted both the fundamental similarities and the apparent differences between these reactions. The similarities may be stated in general terms as follows: In both instances reactions are produced by substances which may or may not have any inherent toxicity; the reactions occur in sensitive or susceptible individuals; the severity of the reaction depends more upon the degree of that susceptibility than upon either the inherent toxicity or the dose of the substance producing it; and the character of the reaction is related to the susceptibility of the individual and is not a specific property of the provoking substance. The apparent differences may be stated as follows: Anaphylaxis is invariably dependent upon a known sensitization to an antigen which is usually protein in nature while allergy may apparently exist without recognizable sensitization and be related to non-protein substances. In anaphylaxis the sensitive state is relatively temporary while in allergy it tends to persist throughout life. The anaphylactic reaction involves an antigen-antibody reaction while the allergic reaction may or may not involve recognizable antibodies. Lastly an anaphylactic reaction may be followed by a state of complete refractoriness while the allergic reaction is followed by only a partial desensitization.

The reaction of anaphylaxis and its relationship to immunity is sufficiently intriguing in its own right to have prompted a prodigious amount of study and investigation. I think it probable, however, that many workers have been stimulated with the hope that a partial or complete solution of the experimental problem would contribute to the solution or management of the clinical problem. It is with such a hope that I discuss this question. Within recent years a partial solution of the anaphylaxis problem, with respect to its mechanism, has been made. It seems not untimely to consider the implications of this work, so I wish to present a brief résumé of its development.

In 1910 Manwaring [2] reported some experiments in which a cross circulation was established between a normal dog and a sensitized animal. He reported that the injection of the antigen into the latter resulted in anaphylactic symptoms in both animals and concluded that some blood-borne agent was necessarily implied as the mediator of the symptoms to the normal animal. At about this same time Dale and Laidlaw [3] called attention to the similarities between histamine intoxication and anaphylactic shock so

* Received for publication April 10, 1939.

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that inferences as to the chemical nature of the blood-borne agent in anaphylactic shock can be said to date from this period. In 1917, however, Weil [4] virtually dispelled all hopes of this kind of a solution to the anaphylaxis problem. He challenged the validity of cross circulation experiments by pointing out that a marked fall in blood pressure in one animal from any cause would necessarily cause a similar fall in the other by the simple process of exsanguination and also that suggestive results were frequently probably due to incompatibilities between the bloods of the two animals. He also reported that withdrawing blood from anaphylactic animals and injecting it into normal animals had negligible effects. He concluded that a humoral theory of anaphylaxis was untenable. The weight of his authority was such that conflicting evidence was largely disregarded for a considerable time. As a by-product of his work it became rather generally accepted that the important reaction in anaphylactic shock is not the reaction between the antigen and the circulating antibodies, but the reaction between the antigen and the fixed tissue cells.

In 1925 Manwaring, Hosepian, O'Neill and Moy [5] reported some interesting and suggestive experiments. They vascularly anastomosed the hind quarters of a normal dog to a sensitized one and noted that the urinary bladder and intestine of the normal animal contracted when anaphylactic shock was induced in the sensitized animal. Since this could not be explained by the nonspecific effect of the fall in blood pressure, it seemed necessary to interpret some smooth muscle stimulating agent as being concerned. Because of some negative experiments with supposedly immunized tissues they [6] were led to conclude that the agent was a sort of secondary antigen presumably of protein nature.

Meanwhile the studies of Abel and Kubota [7] and of Best, Dale, Dudley and Thorpe [8] had shown that histamine is a normal constituent of many tissues, and Lewis [9] had reported circumstantial evidence indicating that a histamine-like substance is apparently liberated in the skin by certain kinds of injury. Considering the evidence available at the time, Dale in 1929 [10] reaffirmed the histamine theory of anaphylaxis. Experiments to substantiate this theory were soon forthcoming. In 1930 and 1931 Watanabe [11] showed that the content of histamine-like substance in guinea-pigs' lungs and in dogs' livers is strikingly decreased when these respective animals are subjected to anaphylactic shock. In 1932 Dragstedt and Gebauer-Fuelnegg [12] reported the detection of a histamine-like substance in the blood and lymph of dogs during anaphylactic shock and Bartosch, Feldberg and Nagel [13] found a similar substance in the perfusate from guinea-pigs' lungs. In 1936 Dragstedt and Mead [14] reported the definite identification of the histamine-like substance as histamine. Of more importance they [15] showed that in the dog the amount of histamine liberated during the anaphylactic reaction is adequate to account for the severity of the reaction and is thus a definitely operating factor and not just an incidental by-product. That histamine is liberated during the anaphylactic reaction in dogs and in

guinea-pigs has now been confirmed by a number of workers,[16] so that it can definitely be stated that the histamine theory has been verified in more than one animal species.

During the last two years, Eagle, Johnston and Ravdin [17] and Waters, Markowitz and Jacques [18] have proved that the incoagulability of the blood which occurs during anaphylactic shock is due to the liberation from the liver of an anticoagulant probably identical with heparin. It is thus clear that the dominant manifestations of anaphylactic shock in experimental animals are attributable to recognizable agents which were initially contained within the fixed tissue cells of the sensitive animal and which were discharged from these cells in some manner subsequent to the injection of the antigen.

Since these results are so readily demonstrated with methods now available it seems appropriate to comment on the negative results of Weil and others who have looked for active agents in the blood of anaphylactic animals. Weil reported that exsanguinating dogs during anaphylactic shock and transfusing the blood into normal animals gave negative results. On studying the protocols of Weil's experiments, his negative results are readily understood. Blood collections were never made less than 20 minutes after the shocking dose of serum and in most instances considerably later. The transfusions were then made into animals under ether, which would mask the minor symptoms of vomiting, etc., while no records of blood pressure effects were made. Also of importance is the fact that the blood was injected slowly and intermittently over a period of a half-hour or so. We now know that the histamine is liberated promptly after injection of the antigen and that it then disappears very rapidly from the plasma of the circulating blood. Consequently there was probably little or no activity in the blood samples that he tested in addition to the fact that his method of determining activity was not at all delicate. The negative results of other investigators have in general a similar explanation.

I have purposely stressed these remarks because a number of recent writers on the subject of anaphylaxis have failed to appreciate the definitive character of the experimental evidence that has been reported. It should also be pointed out that the present evidence respecting the rôles of histamine and heparin as secondary operating agents in anaphylactic shock, does not exclude the possibility of other presumably less significant agents being similarly liberated and related to certain features of the symptomatology.

Having worked out technics by which agents responsible for the major manifestations of anaphylactic shock could be detected and incriminated, the attention of various investigators was directed to various other intoxications having some similar aspects in symptomatology. Experimental evidence of various kinds has accumulated which indicates that certain snake venoms,[19] bee venom,[20] staphylococcal toxin,[21] as well as certain inorganic poisons such as mercuric chloride,[22] can produce a cellular injury which results in a liberation of histamine. For some of these the circumstantial

evidence that the liberated histamine is a contributory factor in the symptomatology is fairly convincing. With others the direct toxicity of the substance obscures any such analysis. We [23] have made an extended study of peptone reactions and since in this instance there is no complicating factor of direct toxicity on the part of the substance which provokes the reaction, I shall deal with this in more detail. The intravenous injection of peptone solutions into dogs results in a reaction which is virtually indistinguishable from that occurring in acute anaphylactic shock. We have been able to demonstrate that this reaction is accompanied by and due to the liberation of histamine just as is the case in anaphylactic shock. This has now been confirmed.[24] Also it has been reported by Quick [25] and by Waters, Markowitz and Jacques [18] that heparin is likewise liberated during the peptone reaction. Thus it is clear that peptone shock is similar to anaphylactic shock in mechanism as well as in its symptom complex.

If the general similarity between experimental anaphylaxis and clinical allergy has been considered sufficiently close to warrant the hope that lessons learned from the former could be applied to the latter, it seems equally appropriate to view such reactions as that of peptone as having their clinical counterparts. A consideration of some of the characteristics of peptone reactions suggests that in some respects they are more closely comparable with corresponding features of certain allergic reactions than is the anaphylactic experiment. It has long been known that for the production of peptone shock, no preceding sensitization procedure is necessary. The sensitivity occurs spontaneously and so far as has been determined is not dependent upon antibodies of any sort. A certain percentage of animals (approximately 10 per cent of dogs in our experience) is naturally refractory, or conversely it can be said that a certain percentage of animals is spontaneously sensitive. We have recently found that newly born puppies may be sensitive as well as very old dogs, so that the sensitivity in a given animal presumably tends to last throughout life. The injection of a peptone solution is followed by a limited degree of desensitization which differs from that in the anaphylactic experiment by being less regularly produced, less complete and of shorter duration. These features of the peptone reaction have a surprising similarity to the characteristics of certain allergic reactions which have been listed as differentiating the latter from experimental anaphylaxis.

The evidence indicates that various substances may produce directly the same kind of cellular injury and after effects as can be produced by antigens acting indirectly through antibody reactions. Certain experimental reactions of this sort have a greater resemblance to the clinical reaction of allergy than has the anaphylactic experiment. If reasoning by analogy is warranted, this means that we must view these reactions as a whole and that we can not necessarily expect to modify or control all of them by the same methods.

I would therefore like to schematize these reactions for the purpose of

considering some of the various theoretical methods of modifying or controlling them that such a schema suggests.

A. Antigenic allergen—via antibodies—acts on sensitive cells to liberate histamine, heparin and possibly other agents, which in turn act on responsive or reacting cells to produce characteristic effects.

B. Non-antigenic allergen acts on sensitive cells to liberate histamine, heparin and possibly other agents, which in turn act on responsive or reacting cells to produce characteristic effects.

I am visualizing Schema *A* as applying to experimental anaphylactic shock as well as certain allergic reactions and Schema *B* as applying to experimental peptone shock and certain other allergic reactions. In this schematization the term " allergen " is used with reference to any substance which may provoke reactions of this type and is not synonymous with the term " antigen " which implies a capacity to stimulate antibody formation. The term " sensitive cell " refers to those cells with which the allergen reacts, and the term " responsive cell " refers to those cells, etc., upon which the liberated products from the sensitive cells react. It is very likely that in many instances the sensitive cells are identical with the responsive cells. At first glance there may be something anomalous in the conception of a cell containing in its interior a physiologically active substance which produces no effect until it goes outside the cell, when it may then profoundly influence its former abode. There is nothing startling about this, however, for from what we know about the mode of action of drugs upon cells, in most instances it seems likely that they act upon cells by producing effects upon the cell surface. It has been experimentally demonstrated, for example, that certain drugs may be injected intracellularly without producing the effects which they readily do when applied to the cell surface.

Assuming that a chain reaction of this kind may be vulnerable at any link, it should theoretically be possible to modify or control the reaction by procedures which primarily affect (1) the allergen, (2) the antibodies, (3) the sensitive cells, (4) the liberated products, or (5) the responsive cells. By eliminating or altering the allergen the reaction is avoided rather than modified or controlled. The usual desensitization procedure probably acts upon or through the antibody mechanism. That it is not invariably successful suggests the possibility that some of the reactions in which it fails may belong to a non-immunologic category such as we have indicated. If so, it seems important to consider the theoretical possibilities with respect to the third, fourth and fifth links in the chain. With respect to the sensitive cells it is theoretically possible to breed them out, excise them, alter their permeability, or deplete their store of active substances. With respect to the liberated agents it is theoretically possible to inactivate or neutralize them. With respect to the responsive cells it is theoretically possible to render them insusceptible to the liberated agents either by the development of an acquired tolerance or by preëmpting the cell receptors with a chemically similar but physiologically inactive blockading substance. Or it is

possible to use drugs which are pharmacological antagonists to the liberated products and which either reduce the reactivity of the responsive cells or influence them in opposite directions.

It has been an interesting study to go through the long lists of agents which have been reported to be beneficial in experimental anaphylaxis and in clinical allergies respectively. It has long been recognized that these diverse substances have had no single common denominator of pharmacological action. This very fact seems to me to substantiate the theory that these reactions have several and varied vulnerable sectors. With the schemata outlined here an intelligible answer can be given in many instances as to why totally dissimilar substances have shown more or less equivalent beneficial effects. A critical survey of the literature indicates that most of the therapeutic agents employed have had only a limited effectiveness. Many of them have been employed purely empirically, however, and perhaps with a better understanding of the purpose for which they are used, better results may be obtained. It is also clear that a number of the theoretical possibilities suggested here have not as yet been explored. Some of them, to be sure, are neither practical nor feasible, but it may be hoped that others may afford some additional means of modifying or controlling these puzzling reactions.

Summary

There is experimental evidence to indicate that certain foreign substances, not necessarily protein in nature, can produce the same kind of reactions in experimental animals upon their initial administration, as are produced by antigenic agents after a prior sensitization. The possibility that some of the allergic reactions seen clinically are similarly provoked directly by foreign substances is visualized, and the implications of this upon the problem of management are suggested.

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THE VALUE AND SIGNIFICANCE OF THE TUBERCULIN TEST*

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THE tuberculin test is today a commonly employed procedure. As an aid in the diagnosis of tuberculosis, it is being used routinely by the specialists, the general practitioners, and by those concerned purely with the preventive aspect of the disease. Mass testing was first introduced by the veterinarians in their search for bovine tuberculosis in herds. Mass testing of groups of the population is at present an indispensable feature of most antituberculosis programs.

As a test for tuberculosis, tuberculin has been employed in a variety of ways. At first it was given subcutaneously. The ophthalmic test of Calmette and Wolff-Eisner in which tuberculin was applied to the conjunctiva was discarded in preference to Moro's inunction test. Several modifications of this test are now being advocated on the grounds of simplicity of technic and to avoid lay objection to the distasteful needle. The patch test is now gaining in popularity.[1] In sensitivity the patch test corresponds to the Pirquet or to a Mantoux dilution of 1–10,000. The use of one strength tuberculin and the questionable absorption of tuberculin through a thickened epidermis fog the accuracy of this test. A negative patch test should be followed by a test using second strength P.P.D. At present the von Pirquet and the Mantoux are the most frequently used methods. The Pirquet is done by scarification of the skin under full strength tuberculin. The Mantoux is performed intradermally with diluted tuberculin. It is more exact than the Pirquet as the quantity can be accurately measured. It also gives a better cosmetic result. It has been said that the Pirquet is reliable in disclosing past tuberculous infections of a nature to provoke radiographically demonstrable lesions in the chest; whereas, the Mantoux test may be positive in the absence of any demonstrable infection.[2] In the Florida program, we use the Mantoux intradermal test with P.P.D. in two strengths exclusively.

Formerly, old tuberculin, known as O.T., was injected in dilutions varying from 1 in 10,000 to 1 in 100. O.T. was first introduced by Koch in 1890—eight years after the discovery of the tubercle bacillus. It is an exotoxin in the form of a filtrate obtained from a culture of virulent human type bacilli in bouillon. The presence of non-specific protein in the form of peptones is likely to cause pseudo-reactions.

* Received for publication May 16, 1938.
Presented at Polk County Medical Society, Lakeland, Florida, January 12, 1938; Suwannee River Medical Society, Mayo, Florida, February 11, 1938; The Annual Conference of The Florida Tuberculosis and Health Association, Orlando, Florida, April 26, 1938; Duval County Medical Society, Jacksonville, Florida, May 2, 1938.

Consequently, we are now employing purified protein derivative tuberculin, called P.P.D. It can be obtained in five, ten, or one hundred test sizes. It is marketed in tablet form in two strength doses with a sterile buffered diluent, consisting of normal saline and 1 per cent phenol, to be added at the time of its use. The first strength (0.00002 mg.) is the initial dose and is equivalent to a 1:25,000 dilution of O.T. If no reaction is obtained, the second strength (0.005 mg.) is employed. The latter is 250 times as strong as the first strength. Dilutions of P.P.D. will keep for three days on ice, but should then be discarded. P.P.D. is favored over O.T. because of its greater efficiency and because it is a purified and more easily standardized material. Dr. Esmond Long of the Phipps Institute in Philadelphia is working on a suitable single dose preparation of P.P.D. which will obviate the necessity for two strength tests.

The technic of the Mantoux intradermal test is similar to that of the Schick test. The skin on the flexor surface of the forearm is cleansed with 95 per cent alcohol and allowed to dry. A 1 c.c. tuberculin syringe is used. The syringe should be used only for that purpose. No matter how well sterilized, a syringe which has been employed for the tuberculin test will often produce false reactions if used for the Schick test. A needle with a sharp short bevel, gage 26, is best. The needle is inserted almost parallel to the skin and 0.1 c.c. of the tuberculin is injected. This will produce a small white bleb showing that the injection has been made into the skin and not under it. If the injection is made subcutaneously, no local reaction may appear and a generalized febrile reaction may result. No dressing need be applied to the area.

The site should be examined in 48 hours. The reaction, if any, appears in 12 to 24 hours; reaches its maximum in 48 hours; and tends to disappear gradually after 72. Pseudo-reactions usually appear sooner. Reactions reaching a maximum after 72 hours are usually due to superimposed infection caused usually by scratching. If such infection has occurred, the usual signs of lymphangitis and adenitis may be observed. Often, a purely erythematous reaction may occur after 72 to 96 hours.

A positive tuberculin reaction is a red edematous area at the site of injection. Erythema, in itself, does not constitute a positive result. There must be induration, at least five mm. in its shortest diameter, before a reaction can be called truly positive.[3] This can be felt as an area elevated over the surface of the surrounding skin. As the relationship between the intensity of the reaction and the degree of tuberculous activity, the time of infection, or the clinical course which the disease will pursue has not been proved, it is not necessary to classify the intensity or degree of the positive reaction. A reaction is positive, negative or doubtful. A positive reaction indicates that tuberculo-allergy is present; that is, that the tissues are hypersensitive to the products of the bovine or human type tubercle bacillus.

To appreciate the full significance of a positive tuberculin reaction, it is necessary to review briefly the pathogenesis of tuberculosis.

There are two types of tuberculosis: the childhood and the adult. As either of these types may occur in children or adults, it would be less confusing to refer to them as the first infection type and the reinfection type respectively. The reinfection type will not occur unless there has been a previous first infection type regardless of the age of the individual.

We are born free of tuberculosis as the disease is not inherited. When tubercle bacilli invade the body for the first time, a series of changes occurs. The lipoid capsules of the bacilli are dissolved liberating tuberculoprotein. With liberation of this substance, the tissues are sensitized. This period may last from two to six weeks after which a positive tuberculin test can be secured.[4] The tissues become allergic and will react in a hypersensitive manner to further contact with tuberculoprotein.

Entrance of the bacilli may be effected through any of the avenues of the body but, by means of inhalation, the lung is the commonest portal. The organisms are carried to the subpleural surface of the lung parenchyma and tubercle formation takes place there, producing what is known as the Ghon tubercle. The glands at the hilum draining that area soon become involved in the process. This constitutes the primary complex. It takes two to six weeks to develop and is a pathognomonic morphological entity. It occurs only once in each body and marks the first entrance of the bacilli.[5] This series of changes is the genesis of the first infection type of tuberculosis. The condition is really a pulmonary tuberculosis, but usually runs a benign course if further infection stops and general resistance is maintained. Calcification occurs and no permanent damage results. But it is well to remember that living bacilli may be incorporated in the calcified matrix which, many years afterwards, may be the source for reinfection. It usually takes two to four years for calcification to cast a recognizable shadow on the roentgen-ray.[6] Consequently, a negative chest plate in a positive tuberculin reactor may be due to the fact that the time element has not been sufficient for the lesion to become manifest radiographically. The tuberculin test with P.P.D. detects approximately three-fifths of all cases of primary tuberculous infection. The roentgen-ray is only slightly more efficient on a percentage basis.

The reinfection type of tuberculosis may occur immediately following the first infection or many years later by endogenous or exogenous reinfection. The soil is no longer virgin. Now, the tissue is allergic, and in the presence of tuberculoprotein, will flare up in an outrageous manner. The amount of tissue destruction will depend upon the virulence and dosage of the organisms and upon the resistance and immunity of the host. This is the classical type of tuberculosis, with caseation and cavitation.

Once the tuberculin test is positive it usually remains so throughout life, although the degree of the reaction may vary from time to time. The tuberculin reaction may even show a daily variation apparently due to periodic changes in vascular and tissue permeability.[7] However, the test may become absolutely negative under certain conditions. In the acute

stages of measles and scarlet fever, sensitivity to tuberculin may be greatly decreased or completely absent. This anergy may last one to two weeks after the rash appears.[8] During pregnancy anergy may be present. In very acute tuberculosis and in moribund cases,[9] the resistance is exhausted and the tissues are flooded with tuberculoprotein to such a degree that the tuberculin test will elicit no response. During the incubation or latent period when the primary complex is forming the test will be negative. About 5 per cent of individuals will show radiographic evidence of old tuberculous foci and a negative tuberculin reaction. This anergy is probably due to lesions long healed in which the calcified foci contain no living organisms.[10] As calcification and healing take place, there is a decrease in the allergic response.[11] Hence, in the latter stages of the primary infection, a feeble cutaneous reaction to tuberculin, denoting a low degree of tuberculous allergy, is generally obtained. A test followed by a general reaction (febrile, etc.) is suggestive of an active tuberculous lesion.

A positive test tells us that tubercle bacilli have invaded the body—tuberculous infection has been established—but it does not tell us if destructive disease is present. It indicates with certainty that the first infection type has occurred but to discover the presence of reinfection type a roentgen-ray of the chest is necessary. We know the superiority of the roentgen-ray over other methods of examination in arriving at a diagnosis of early tuberculosis. Consequently, all positive tuberculin reactors should be roentgenographed.

The tuberculin test should be used for the recognition of infection at the earliest possible moment. If every child were tested periodically from infancy, the time and source of the infection could easily be ascertained.[12] It is for this reason that we recommend physicians to make the test a routine part of the examination of all children. If the test is negative it should be repeated at least once yearly until the adolescent period is passed. The interval between the last negative and first positive reaction is the time when the child was exposed to and infected by an open case of tuberculosis. By tuberculin testing and roentgen examination of the child's contacts, the unknown or unrecognized case can be discovered at a curable stage and a stop put to the further spread of the disease. Objection to repeated tuberculin testing on the grounds of possible sensitization of the child to tuberculoprotein has been raised. However, such sensitization from the ordinary use of tuberculin for skin testing purposes does not appear likely,[13] although it may increase an already existing slight sensitivity.[14] At times the site of a previous test in a positive reactor may show erythema following a re-test in some other area months afterwards. In the larger northern cities, the incidence of positive reactions is the following: at five years of age 15 per cent react, at seven years 20 per cent, at ten years 40 per cent. The rates are much lower in most southern states.[15] In this state we have tested nine thousand school children from 15 to 20 years of age. In the white group 29 per cent were positive reactors. The rate for the negro

group was 10 per cent higher. Almost 2 per cent of these positive reactors showed roentgen evidence of reinfection type tuberculosis.

In infants and children up to four years of age a positive reaction can be taken as a sign of a relatively active process, since it takes two to four years for the lesion to become arrested.[16, 17] The tuberculosis mortality rate in this age group is very high as these children are practically without defense against infection and reinfection, living, as they do in most cases, with a tuberculous parent.[18] A study of infants under two years of age with positive reactions gave these results: 13 per cent of the white and 31 per cent of the colored infants died within five years. Seventy per cent of these deaths occurred within the first year of observation.[19]

Above five years of age there is greater opportunity for extrafamilial exposure. However, the home and the school must be considered the most fertile sources of the infection. It is there that prolonged and intimate exposure to massive dosage of bacilli is most likely to take place.

As we ascend the age groups we find that the tuberculosis morbidity rate increases proportionately with age; whereas, the mortality rate remains fairly low until puberty when it accelerates until it reached a peak in the 20 to 35 year age period.

A school child with a positive tuberculin test is 27 times more likely to develop a manifest reinfection lesion than a colleague without primary infection.[20] Children under five years with positive reactions should be supervised for a time sufficient to indicate by roentgen-ray that no lesion exists—usually until seven years of age if the source of the infection has been removed. If the source still exists supervision should be continued until 25 years of age. Adolescents and young adults 15 to 20 years old with positive reactions and a history of exposure to an open case within two years should be observed until they are 25 regardless of roentgen findings.[21] It would be best if all positive reactors with negative chest plates were to be refilmed yearly until the adolescent stage was past.

Dr. J. A. Myers, president of the National Tuberculosis Association, believes that the best criterion of the tuberculosis problem in any state is the incidence of positive tuberculin reactors rather than morbidity and mortality rates.

The tuberculin test is of great value in differential diagnosis. It has been said that, except in the anergic group, a negative test rules out tuberculosis as definitely as tubercle bacilli in the sputum rule it in.[20]

Tuberculin testing is of such practical importance that it is ranking in general practice equally with small pox vaccination and the Schick test.

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THE RELATIVE VALUE OF THE BASAL METABOLIC RATE, VELOCITY OF BLOOD FLOW AND CREATINE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF GRAVES' DISEASE AND ALLIED CONDITIONS *

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THE differential diagnosis of Graves' disease from a group of conditions, which occasionally simulate it in symptomatology, not infrequently presents a difficult problem. Whereas typical cases of Graves' syndrome present no difficulty, since the clinical picture is so characteristic, borderline cases in which the symptomatology is not clearly delineated are not so easy to differentiate. We refer to cases of inactive Graves' disease, autonomic imbalance, menopause with autonomic imbalance and hypertension, simple goiter and cases of essential hypertension.

Because these cases are not as readily diagnosed on clinical grounds, efforts have been made by previous workers to find some objective laboratory determination which would simplify the differentiation of these cases from true instances of Graves' syndrome. The finding most commonly relied upon has been the determination of the basal metabolic rate. More recently there has been introduced by Shorr the creatine tolerance test.[1]

In this study we have investigated the comparative value of such determinations as the basal metabolic rate, the creatine tolerance test, and in addition the velocity of blood flow (saccharin method) [2] as aids in diagnosis.

Eighty-seven patients studied by us over a two year period were classified in the following groups (tables 1 to 5).

1. Graves' disease
   - (*a*) Active—11 cases
   - (*b*) Inactive—6 cases
2. Borderline cases
   - (*a*) Autonomic imbalance—49 cases
   - (*b*) Menopause with autonomic imbalance and hypertension—7 cases
3. Allied disorders
   - (*a*) Essential hypertension—10 cases
   - (*b*) Non-toxic goiter—6 cases

   } 14 patients (2 had both conditions)

The cases of active Graves' disease had the characteristic symptomatology. Most of them complained of nervousness, palpitation, sweating, emotional and vasomotor instability, and weight loss. The majority had a

* Received for publication February 12, 1938.

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TABLE I
Graves' Disease

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	Creatine Tolerance Test				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
57	M	35	+59 +41 +52 6[1]	10¾	0	.050	.640	.950	95
58	M	52	+37 +31 *+20* *+10* *+28* *+13* − 8 +31 +31 +41 +50 *+29* *+31* + 9[2]	10 12¾ 10½	.185 .075	.210 .365	.880 .800	.750 .390	98 71
59	F	58	+48 *+17*	11	.145	.775	.670	.615	37
60	F	45	+66 +52 +48 *+42* *+25* +43 +24	10½ 9¾ 11¼	0 0 .455 0	.190 .210 .905 .305	.740 .570 .365 .805	.945 1.170 .795 .880	81 79 55 69
61	M	25	*+47* *+51* *+41*[2] + 9[2]	5½					
62	F	21	+35 +49 +37 *+21* + *8* +50[2] 0 +25	10	*.440* .100	*.705* .400	*.530* .710	*.445* .850	*74* 70
63	F	19	+15 +54 *+62* *+64* *+38* *+13*[1] + *9*	6 6½ 7½ 7½	.050 .180 .095	.400 .695 .115	.435 .815 .755	.670 .695 .785	65 48 98
64	F	56	+36 +29 +20	11 11½	.045	.560	.450	.560	49
65	M	42	+60 +16 +51 *+60* *+45*[2] *+15*[2] + 4[1] + 9	8½ 10½	.175 .025 0	1.190 .645 .125	1.150 .840	.970 .900	1 87
66	F	69	+51 +29 +43 *+34* *+24* *+29* *+22* *+13*[2] *+22* *+20* + 7 +47 − 4 +23	8 9½ 8½ *10* 7½ 8½	.390 .320 .305 .096	1.885 .390 .340 .380	.755 .700 .765 .720	.765 .665 .790 .710	60 93 97 72
67	F	30	+62 +48 *+11* *+28* +43 +48 +19[2]	7 6¾ 7¼	.260	.395	1.060	1.045	86

TABLE I (*Continued*)
Inactive Graves' Disease
Asymptomatic

68	F	31	−13	15	.130	.420	.790	.830	71
69	F	38	+66 +37 +43 +31 +45 +54 +27 +25[1]	10 12	0	.175	.920	.975	82
70	F	27	− 4 + 9	10	.055	.210	.775	.675	85
71	F	39	+14	10½	.050	.815	.975	.895	23
72	F	42	+ 9	12					
73	F	48	+48 +47 −10 + 6 −10 − 6	14¼	0	.055	.900	.850	94

[1] After operation.
[2] After Lugol's solution.
Figures in italics signify tests made while patient was an in-bed patient in the hospital.

definite tremor and tachycardia. A minority had, in addition to the foregoing, exophthalmos, lid lag, or an enlarged thyroid gland. The inactive cases were instances rendered non-toxic by thyroidectomy or roentgen-ray therapy. Four of these cases continued to present symptoms, chiefly of vasomotor and emotional instability (autonomic imbalance).

The complaints of patients comprising the group of autonomic imbalance were referable to the involuntary nervous system. Thus the outstanding

TABLE II

Autonomic Imbalance

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	Creatine Tolerance Test				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
1	M	36	+20 +18 + 2	9 11½ 10½					
2	F	39	+37 +65 −15	8¼ 9½ 9	.135	.415	.670	.605	72
3	F	35		9½	.055	.635	.970	.720	42
4	F	30	+ 4	9½	0	.090	.900	.960	91
5	F	26	−10	8½ 8½ 10¼ 8½	0	.330	.640	.385	67
					.030	.135	.365	.240	89
6	F	46	+38 +15	11½	.160	.730	.800	.970	43
					.230	.330	.860	.900	90
7	F	31	+33[1]	9	.265	.330	1.150	.850	94
8	F	36	+11 +43	7½ 7¼ 7¾	.105	.780	.535	.580	33
9	F	29	+42 +13	11½	0	.630	1.270	.930	37
10	M	30	+ 3	11¾	.095	.190	1.845	1.160	91
11	F	45	+ 3	13	0	.360	.500	.530	64
12	F	59	+45 − *2*	*11*	0	.165	.750	.505	83
13	M	36	− 3	17	0	0	1.040	1.280	100
14	F	37	+24 +23 +36 +15	9½ 10 13¼	.055	.700	1.275	1.240	36
15	F	40	+ 9	12	0	1.125	.955	1.290	87
16	M	35	+22 +42 +23	11 9½ 10¼	.695	1.000	1.270	1.240	70
			+17 +10 + 5		*.070*	*.655*	*.910*	*.990*	*41*
			+ 4 + *2* +31 +25 +14	9½	*0*	*.180*	*1.310*	*.950*	*82*
					0	.335	1.590	1.850	66
17	F	45	+36 +49 *+20* + *5* +31 +11	11	.205	1.220	1.120	1.165	75
18	M	44	+17 + 1	9 8	.285	.340	.940	.785	95
					.180	.190	.835	1.690	99
19	F	44	0	9½ 11	.090	.380	.800	.710	71
20	F	34	+ 6 +28 +57 − 5 +20						
21	F	26	+114 +31 +40 +17 +47[2] + 3[2] + 5	8 11 8¾ 9¼ 10[2] 9[2] 10[2]	0	.135	.560	.830	86
22	F	29	+64 *+37 +30* *+19 +25 +20* + 5	12½	*.170*	*.220*	*.440*	*.245*	*95*
					.155	*.605*	*.880*	*.660*	*55*
					0	.170	.880	.680	83
23	F	59	+33 + 2 − 6 + 1	10 10 9¾	.595	.935	.895	.945	66
					.210	.875	.855	.875	33

TABLE II (*Continued*)

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	Creatine Tolerance Test				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
24	F	30	+11 −11	8¾ 10 7 8½	0	.150	.790	.620	85
25	F	19	− 3	11½	0	.120	.740	.690	88
26	F	31	+46 +30 +35 +21 +54 +23 + 9	8 7½ 7½ 7 7 7½	.200	.370	1.470	1.120	83
27	F	33	+22 +38 +15	9¾ 9¼	0	.170	1.130	1.090	83
28	F	38	+10		.145	.445	.836	.810	70
29	F	25	+28 +14	8 9½	0	.280	.870	1.050	72
30	F	18	−20 −24	8¼ 8¼					
31	F	23	+24 + 5 +15 + 7	10½ 13	0	.120	.850	1.060	88
32	F	29	+71 +37 +29 + 9	7¾	.060	.495	.750	.825	56
33	F	38	+12	15	.055	.120	1.110	.795	94
34	F	29	+16 +43 + 2	6½ 8½ 8½	.040	.080	.740	.980	96
35	F	40	+ 2	13	.070	.420	.620	1.400	65
36	F	74	+41 +30 +16	12	.120	.100	.470	.660	102
37	M	40	+25 +22	13 12	0	.450	1.200	1.200	55
38	F	28	− 5 +19	12¾	.055	.090	.730	.660	97
39	M	40	+42 + 4	16½	.135	.320	1.025	1.470	82
40	F	37	+23 0	10 13½ 13	0	0	1.450	1.640	100
41	M	43	+21 −16		.165	.520	.985	.860	65
42	F	33	+30 +18 0	11¼ 15	0	.295	.960	.835	70
43	F	40	+10	10	.355	.490	1.415	.730	87
44	F	64	+20 +23 +20 +10	8¾ 15 15½	0	.180	.730	.650	82
45	F	33	+30 +45 + 2	9½ 9	.295	.535	.875	.805	76
46	F	38	+38 +16	9¼ 8½	.080	.340	.500	.430	74
47	F	38	+28 +12 +43	8¾ 9	.065	.196	.745	.885	87
48	F	55	+20 +20 0	12	.130	.400	.830	.600	73
49	F	42	+21 +16 − 8 +31 +18 +56 − 2	10½	.060	.180	.770	1.090	88
					0	0	.850	1.330	100
					0	.365	.625	.475	63

symptoms and signs in these cases were palpitation, dyspnea, tachycardia, tremor, sweating, vasomotor and emotional disturbances, nervousness, anxiety states, episodes of diarrhea, "indigestion," menstrual disturbances, headache and insomnia. Kessel and Hyman [3] have clearly delineated this group and applied to it the term "autonomic imbalance." This entity has been referred to by other authors as Graves' constitution,[4] "forme fruste" of hyperthyroidism, neurocirculatory asthenia, and Basedowoid.

TABLE III
Menopause with Autonomic Imbalance and Hypertension

Case No.	Basal Metabolic Rate	Circulation Time in Seconds	Creatine Tolerance Test				
			Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
			Control Day	Creatine Day	Control Day	Creatine Day	
50	+21 +18 + 5	10 9½ 9 9 9¾	0	.365	1.065	1.100	63
51	+ 9 + 5	9¾	.055	.410	1.275	1.090	64
52	+15 +35 +61 +12	12	.080	.200	.530	.695	88
53	+16 +41 +13 +48	13 13½	.045	.130	.880	.725	92
	+15 +32 +31 +38						
	+33						
54	+ 9	9	.070	.100	.790	.905	97
55	+35 +26	10½	0	.020	1.050	.720	98
56	+36 − 3 +25 − 5	9¼ 10 11	.070	.390	1.250	1.060	68

TABLE IV
Essential Hypertension

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	Creatine Tolerance Test				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
74	F	51	+31 +14	11½ 12 12½					
75	M	15	−28 − 3	10 8¾	0	.165	.920	1.025	83
76	M	55	+25 +10 +19	15	0	.280	1.350	1.210	72
77	F	60	+27 +25 +20	11½ 10	0	.205	.925	.990	79
			+24 +12						
78	F	38	+25 − 4	9¼					
79	F	48	+31 +14	14	.015	.020	.365	.415	100
80	F	42	+26 +10	8 8½	0	.190	1.055	1.090	81
81	F	41	+24	11					
82	M	53	+ 3	11 13½					
83	F	44	0	10	.050	.100	.920	.635	95

The remainder of the patients had essential hypertension or non-toxic goiter. In general the differential diagnosis from Graves' disease was clear clinically, but sufficient objective or subjective manifestations were present to warrant their inclusion as allied diseases.

The clinical and laboratory findings in Graves' syndrome have repeatedly been reported upon, whereas the more prevalent borderline cases have re-

TABLE V
Non-Toxic Goiter

Case No.	Sex	Age	Basal Metabolic Rate	Circulation Time in Seconds	Creatine Tolerance Test				
					Creatine in gm. per 24 hrs.		Creatinine in gm. per 24 hrs.		Retention Per Cent
					Control Day	Creatine Day	Control Day	Creatine Day	
77	F	60	+27 +25 +20 +24 +12	11½ 10	0	.205	.925	.990	79
84	F	15	+27 + 6	11¼ 11	0	.275	.890	.665	72
85	F	48	+18	11¾ 11¼	.255	.380	1.670	1.220	87
					.070	.335	1.235	1.000	73
82	M	53	+ 3	11 13¼					
86	F	26	+13 +18	12	.330	.350	.650	.960	98
					.090	.530	.670	.625	56
87	M	18	− 1	16	.070	0	1.360	1.775	107

ceived considerably less attention. The latter form, in our experience, an important group because they are not infrequently subjected to unnecessary thyroidectomy. Especially prominent in this regard are the cases of autonomic imbalance with or without goiter. Because of this such cases constitute the major portion of our series.

The patients were followed chiefly in the out-patient department but where the clinical diagnosis required further investigation or corroboration they were hospitalized for varying periods.

BASAL METABOLIC RATE

As is well known the basal metabolic rate is uniformly elevated in Graves' syndrome and is reduced by the administration of iodine and by subtotal thyroidectomy. Our experience with this determination in the borderline and allied cases would indicate that initial determinations are frequently elevated and misleading because they are not basal, and that at times repeated determinations with insistence on the most favorable conditions, are necessary before obtaining the true basal rate. Especially does this hold in cases of autonomic imbalance. In some instances we have succeeded in obtaining an accurate (normal) figure only after hospitalization. It is readily seen that an elevated figure obtained in a random determination of the basal metabolism in an ambulatory patient is wholly unreliable. It follows also that in cases where clinical judgment dictates against the diagnosis of Graves' disease in spite of an elevation of the basal metabolic rate, one should adhere to the clinical impression until repeated determina-

tions under ambulatory conditions and, if necessary, after hospitalization fail to register a fall to normal.

Because of the cyclic nature of Graves' disease an occasional patient (cases 58, 62, 67) may show a fall in the basal metabolic rate to well within normal limits after hospitalization and bed rest alone. However, the temporary nature of this finding as well as the presence of other characteristic manifestations leaves no doubt as to the diagnosis.

Circulation Time

According to Blumgart [5] and others the velocity of blood flow is roughly in direct proportion to the basal metabolic rate. It seemed to us that if the velocity of blood flow mirrored the basal metabolic rate the former determination might be of some value clinically if it were less labile than the latter. The determination of the velocity of blood flow as measured by the saccharin method in terms of arm-to-tongue circulation time has not been used as an adjuvant in the clinical diagnosis of Graves' disease. The circulation time was measured by the interval elapsing between the injection of saccharin into the ante-cubital vein and the perception of the sweet taste in the tongue. By this technic, the arm-to-tongue circulation time in health is between nine and sixteen seconds. One hundred and sixty-seven determinations were made in 88 patients. The resulting data, expressed in average figures and ranges, were tabulated as follows:

	No. of Patients	No. of Tests	Average	Range
1. Graves' disease				
(*a*) active.	11	27	9¼ sec.	5½–11 sec.
(*b*) inactive.	6	7	12 sec.	10 –15 sec.
2. Autonomic imbalance.	48	93	10⅝ sec.	7½–17 sec.
3. Menopause with autonomic imbalance and hypertension.	7	14	10½ sec.	9 –13¼ sec.
4. Essential hypertension.	10	16	11½ sec.	9¼–15 sec.
5. Non toxic goiter.	6	10	13 sec.	10¾–16 sec.

These figures corroborate the previous finding of acceleration of the velocity of blood flow in hyperthyroidism. Thus, the shortest circulation time, 5½ seconds, was obtained in a case of Graves' disease with basal metabolic rates of + 47 and + 51 determined during hospitalization. Moreover, the range for circulation times in instances of active Graves' disease is distinctly lower than for other cases in this series. However, when the average is taken, the figure is found to be a low normal. On the other hand, the group with inactive Graves' disease (even though symptoms of instability be present) have a normal range and normal average.

From table 2 it is evident that in instances of autonomic imbalance one not infrequently notes a decrease in the circulation time. However, in the

vast majority of cases the velocity of blood flow is normal. The remainder of cases in this series had circulation times within normal limits.

It is readily seen that while, in general, cases with significantly elevated basal metabolic rates have shortened circulation times, it is impossible to use this generalization for diagnostic purposes in specific instances since the differences in the circulatory measurements are not sharply enough drawn and there is considerable overlapping of the ranges. A further diagnostic limitation lies in the observation that a rapid circulation time in Graves' disease may not be significantly altered after relief of symptoms by operation (case 63) or through the taking of iodine (case 66). On occasions, when discordant figures are obtained for the basal metabolic rate and circulation time these figures may be of value. Thus, in a borderline case (case 44) having a considerable elevation of the basal metabolic rate and a circulation time at the upper limit of normal, one can, in the absence of myocardial failure or venous obstruction, entertain the presumption that the figure for the basal metabolic rate is not reliable, and that the case is probably not one of Graves' syndrome.

Creatine Tolerance Test

Recently there has been introduced a test, by Schorr, based on the previous finding, that patients with Graves' disease have spontaneous creatinuria which disappears on the administration of iodine. This test consists of the administration of creatine by mouth to patients on a creatine-free diet, and the determination of the degree of excretion of this substance. Evidence of a defect in the metabolism is indicated by:

1. Spontaneous creatinuria above 50–60 mg. in 24 hours.
2. Retention of less than 70 per cent of the ingested creatine.
3. Low output of creatine per kilo of body weight.

In another publication [6] we have analyzed in detail our findings after utilization of this test in the differential diagnosis of the cases forming the basis of this report. Tests were performed on 75 patients. Our protocols indicate that use of this test is sharply curtailed by:

1. The occurrence of partially positive tests, viz., spontaneous creatinuria or decreased tolerance, in control cases.
2. The finding of completely positive tests in some patients with autonomic imbalance.
3. The occurrence of completely positive tests in only 50 per cent of the patients with Graves' disease.

Summary

1. A group of 87 patients comprising 17 cases of Graves' disease and 70 cases of allied conditions (autonomic imbalance, menopause, hypertension

and non-toxic goiter) was studied in an attempt to evaluate the comparative value of laboratory aids such as the basal metabolic rate, the circulation time and the creatine tolerance test in differential diagnosis.

2. In borderline cases, initial and at times repeated determinations of the basal metabolic rate may be elevated and misleading. Repeated determinations are required, after hospitalization if necessary, until they register a fall to normal.

3. The determination of the circulation time fails to afford a laboratory aid in the differential diagnosis between Graves' disease and the borderline cases, since the differences are not clear cut enough and there is considerable overlapping of figures for both groups. Only when discordant figures are obtained for the basal metabolic rate and the circulation time, can these tests be of some suggestive value.

4. Our experience with the creatine tolerance test discloses that it is also limited in its usefulness and may give discordant results.

5. Laboratory aids in general are inadequate as absolute criteria in the differential diagnosis between Graves' syndrome and the borderline cases which simulate it. However, the determination of the basal metabolic rate excels the circulation time test and the creatine tolerance test in usefulness.

It would seem that in the last analysis, clinical judgment surpasses in value any of these laboratory aids. The latter should assume a secondary rôle and be employed with distinct knowledge of their limitations and shortcomings.

We are greatly indebted to Miss Mildred Rosenbluth for valuable assistance in the execution of the tests.

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ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING CAROTID SINUS STIMULATION *

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It is well recognized that "vagotonia" may have an important bearing upon several cardiac disorders such as auricular premature beats, heart block, and bundle-branch block. It is also accepted that activity of the carotid sinus reflex, among other things, results in increased vagus effect which may at times aid in controlling paroxysmal tachycardia. If the above facts alone did not indicate the desirability of giving much study to the carotid sinus reflex, certainly recent developments would do so. The fact that Weiss [1] and his associates in three years observed 56 patients who suffered from attacks of unconsciousness due to overactivity of the carotid sinus reflex would alone justify widespread interest in the subject. Smith [2] incidentally has referred to 85 similar cases observed at the Mayo Clinic. For some years Sigler [3] had been making careful and comprehensive clinical observations on the carotid sinus reflex but the description by Weiss and associates of a definite syndrome due to abnormality of the reflex has greatly increased interest in its mechanism. This is especially true because the syndrome they describe had to do with loss of consciousness. As Smith has pointed out, "There is hardly a condition in the field of medicine that disturbs the patient or affects his general morale as much as does the loss of consciousness or a severe attack of vertigo." Medical literature contains many reports which show that a variety of unconscious or syncopal spells formerly classed as epilepsy, narcolepsy or simple fainting may in reality be due to overactivity of the carotid sinus reflex.

Also it is becoming more and more apparent that the functions of the autonomic nerve system, which are as yet little understood, have an important bearing upon a variety of functional and emotional disturbances such as chronic fatigue, mental depression, emotional instability, lack of ambition, Raynaud's disease, angina pectoris and various neuroses. Ferris, Capps and Weiss [1] have recently emphasized the relation of the carotid sinus to the autonomic nerve system and suggested that the carotid sinus reflex offers an excellent opportunity to test the action of certain drugs on the central and motor portions of the autonomic nerve system. The possibilities in this field also make it seem worthwhile to study the cardio-inhibitory aspects of the carotid sinus reflex by means of the electrocardiogram.

No attempt is made here to study any except the cardio-inhibitory effects of carotid sinus stimulation by mechanical means. The depressor type of response accompanied by a fall in blood pressure and the cerebral type of response in which syncope may occur without alteration of heart rate or

* Read at the New Orleans meeting of the American College of Physicians, March 28, 1939.

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blood pressure were not studied. In view of the fact that the cardio-inhibitory response is often quite marked following carotid sinus stimulation, it is rather surprising to find so few electrocardiographic studies of this subject. A partial review of the literature during the past ten years showed only one contribution devoted principally to electrocardiographic changes produced by carotid sinus stimulation. Sigler [4] who had previously made clinical studies of the reflex in 345 individuals reported details of electrocardiographic studies on 50 patients. His study showed the predominant effect to be sino-auricular slowing or standstill and varying degrees of auriculoventricular block. He also observed occasional sinus arrhythmia, ventricular escape and nodal rhythm. Changes in the P-wave were frequent and consisted principally of a decrease in amplitude. Changes in the R-wave, R–T segment and T-wave were rare occurrences. It appeared from his studies that the right carotid sinus reflex had a great effect on the sino-auricular node and the left carotid sinus reflex a greater effect in blocking auriculoventricular conduction. In addition to Sigler's electrocardiographic study of the reflex there have been many reports of electrocardiographic findings in one or several cases [5, 6] that suffered from carotid sinus syncope. Most of these have shown cardiac standstill or inhibition of ventricles to be the mechanism of the seizures. Weiss and Baker [7] have made a study of the carotid sinus reflex in 128 normal individuals and evidently carried out electrocardiographic studies on many of them although details of such study were not reported. Likewise Smith made electrocardiographic studies of many of the 85 cases of carotid sinus syncope to which he has referred. In a general way one may conclude that the findings of all observers agree essentially with those of Sigler.

The group on which the present study was made consists of 67 individuals, most of whom either had definite heart disease or were suspected of heart disease. The group also includes 21 individuals, chiefly student nurses who had no disease. In considering the general incidence of response it is important to bear in mind the presence of these young women, for it is well recognized that females and young individuals show a low percentage of response to carotid sinus stimulation. The ages of the entire group varied from 12 years to 69 years with an average of 39.67 years. There were 20 males and 47 females. Each case in the group had a complete clinical study and standard electrocardiograms before carotid pressure was tested. All tests were made with the patient in the recumbent posture since we were not attempting to reproduce a syncopal attack but merely to test the effect of carotid pressure on the cardiac mechanism. The electrocardiograms demonstrating the reflex response were all taken in standard Lead II with carotid pressure applied for approximately twelve seconds. The beginning and end of carotid pressure application was indicated on the tracing by the lead marker. The method of applying pressure was as follows: With the head tilted slightly backward and away from the side to be tested, the sinus was considered located just below the angle of the jaw

at the level of the upper border of the thyroid cartilage. Pressure was made on the carotid artery just above this point in such a fashion as to compress it against the spine.

In studying the tracings before and after carotid pressure a general inspection of the curves and careful comparison of the form of all waves was followed by measurement of the P–R interval, Q R S interval, P–P interval, and R–R interval before and after pressure. The tracings after stimulation of the sinus were all studied in the light of previous standard lead tracings. This is important, for otherwise slight changes in sinus rhythm or rate observed in the curves after carotid pressure would have been interpreted as due to activity of the sinus although many of the same changes were present in the standard tracings. Also, minor alterations in the sino-auricular rate were routinely disregarded and not considered as the result of the mechanical stimulation of the carotid sinus reflex even though we might grant that these changes were mediated through the vagus nerve. Often it appeared that carotid pressure did no more than accentuate a pre-existent sinus arrhythmia. These slight changes were disregarded.

We first present tracings illustrating the various types of responses that were obtained. (See figures 1 to 8.) Each electrocardiogram shown may present evidence of several kinds of change but best typifies one single response. In the complete tabulation of results, of course, all details of each tracing were recorded.

We shall next consider the incidence of each type of response to carotid sinus (table 1) taking up first the most profound alteration in the cardiac

TABLE I

Incidence of Different Types of Response

	Total	Right	Left
Inhibition of ventricle	3	1	2
Inhibition of auricle	2	2	1
Decreased P-wave	12	9	7
Inverted P-wave	1	1	0
Prolonged P–R	7	5	7
Bundle-branch block	1	0	1
Sino-auricular slowing	49	38	38

mechanism, namely inhibition of the ventricles. Although the present group of patients contained no individuals who clinically suffered from carotid sinus syncope we were able to induce ventricular standstill in three individuals or 4.4 per cent of those tested. This abnormality was induced once by right carotid pressure and twice by left carotid pressure. Each of the individuals so affected experienced slight dizziness or blurring of vision and would probably have become unconscious if testing had been done in the upright posture.

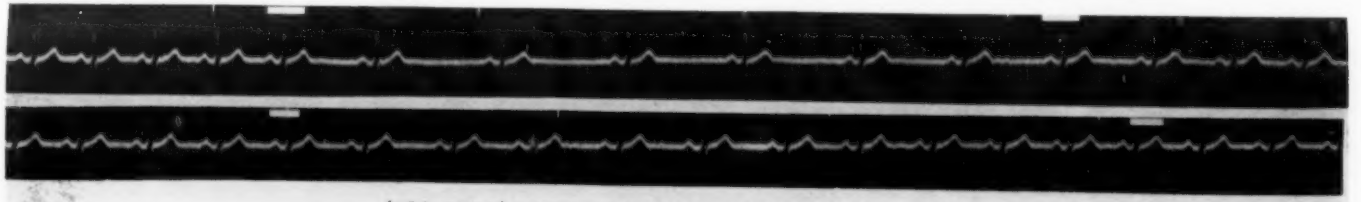

FIG. 1. Case 51 gives us a good example of sino-auricular slowing best seen here following right carotid pressure. The rate prior to pressure was 86 per minute and at the height of response to the reflex the rate was 42 per minute.

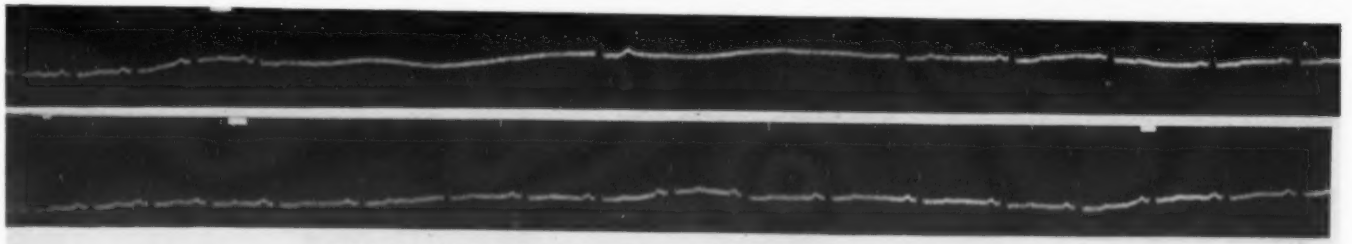

FIG. 2. Case 39 illustrates inhibition of the auricles which persisted for 8.4 seconds following right carotid pressure.

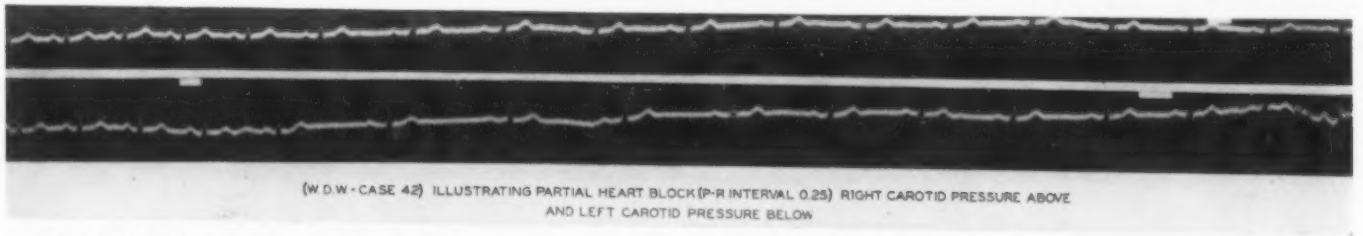
(W.D.W - CASE 42) ILLUSTRATING PARTIAL HEART BLOCK (P-R INTERVAL 0.25) RIGHT CAROTID PRESSURE ABOVE
AND LEFT CAROTID PRESSURE BELOW

FIG. 3. Case 42 shows partial auriculoventricular block with prolongation of the P–R interval to 0.25 second following both right and left carotid pressure.

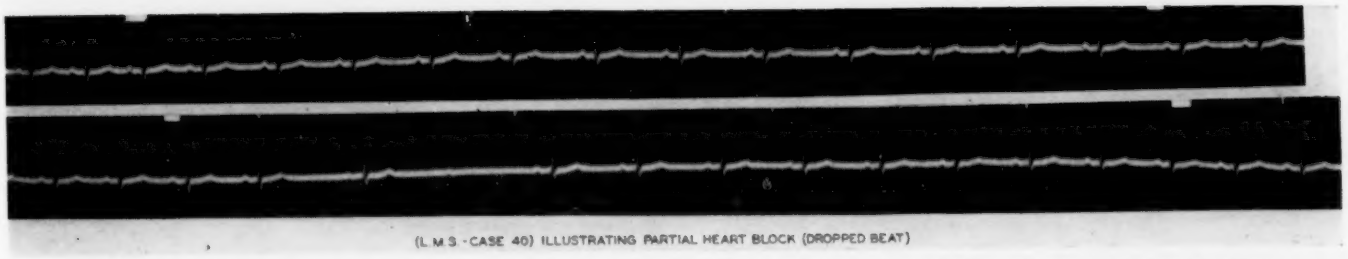

FIG. 4. Case 40 also shows partial heart block with dropped beats following stimulation of the left carotid sinus.

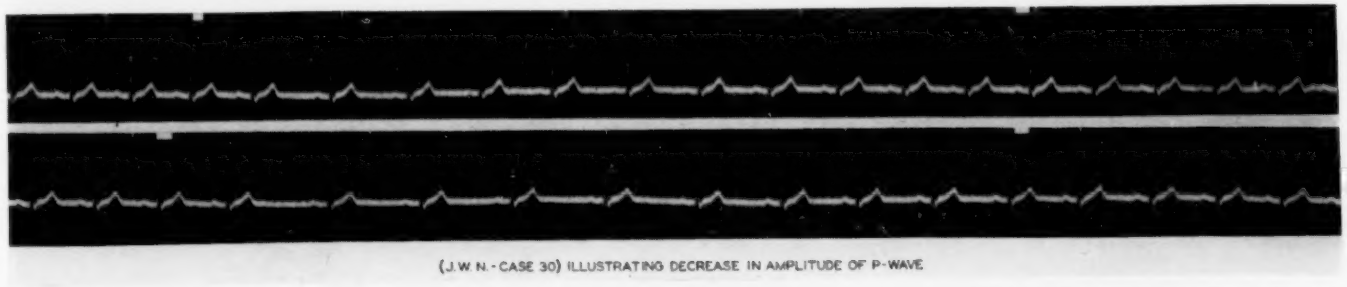

FIG. 5. Case 30 presents a typical example of decrease in amplitude of the P-wave. It may be observed following both right and left carotid pressure.

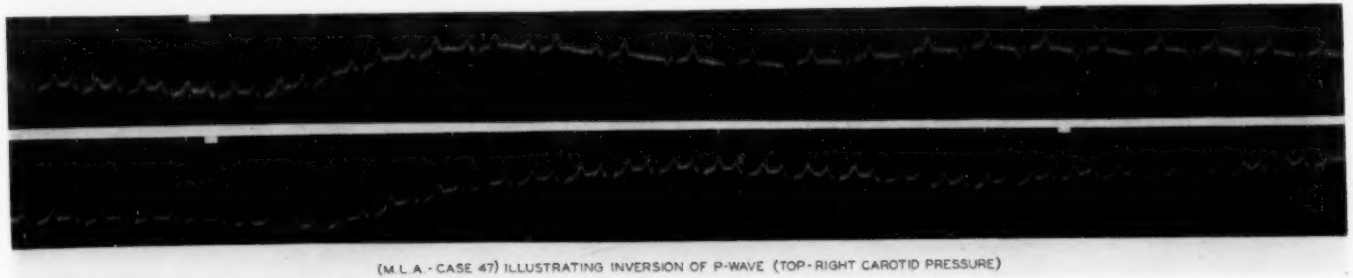

FIG. 6. Case 47 shows a displacement of the pacemaker with inversion of the P-wave following right carotid sinus stimulation.

FIG. 6. Case 47 shows a displacement of the pacemaker with inversion of the P-wave following right carotid sinus stimulation.

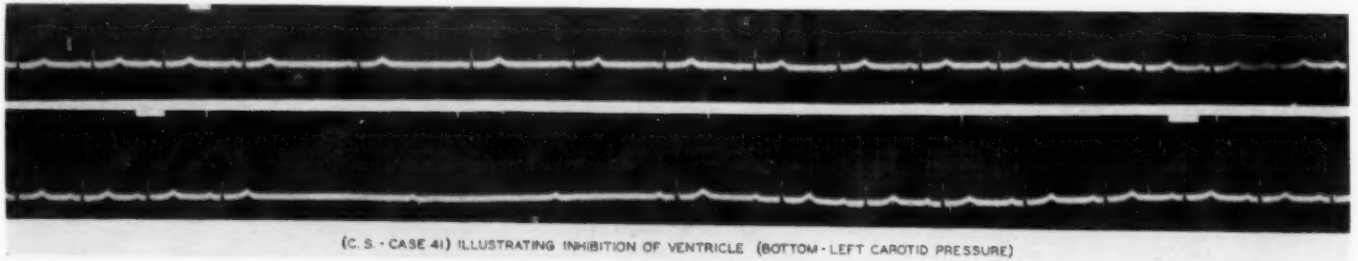

FIG. 7. Case 41 is an example of inhibition of the ventricles which persisted for 5.4 seconds after left carotid pressure.

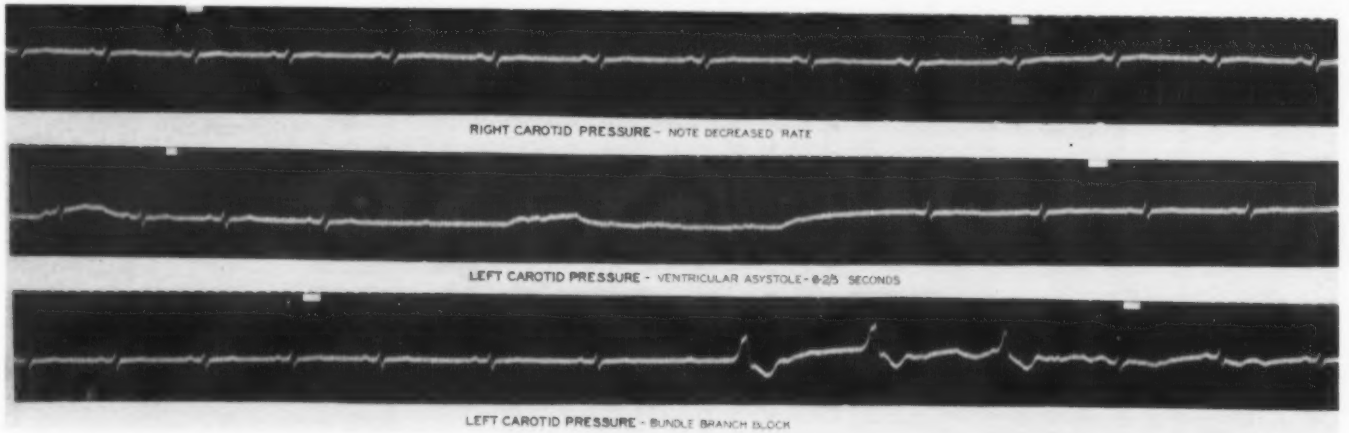
RIGHT CAROTID PRESSURE - NOTE DECREASED RATE
LEFT CAROTID PRESSURE - VENTRICULAR ASYSTOLE - 6.2/5 SECONDS
LEFT CAROTID PRESSURE - BUNDLE BRANCH BLOCK

FIG. 8. Case 67 which has previously been reported [8] shows development of bundle-branch block during stimulation of the left carotid sinus (lower curve). It also shows inhibition of the ventricles for 6.4 seconds (middle curve). In this study no changes were observed in the R–T interval or the T-wave.

Other types of response occurred with the frequency indicated in the table. Inhibition of the auricles appeared three times in two individuals (2.98 per cent), being produced twice by right sided stimulation and once by left sided stimulation. The P-wave showed a decrease in amplitude 16 times in 12 individuals (17.91 per cent), as a result of right carotid pressure nine times and left carotid pressure seven times. There was only one instance of displacement and inversion of the P-wave and it followed right sided stimulation. Various degrees of delayed conduction between auricles and ventricles were found 12 times in seven individuals (10.44 per cent) being the result of right carotid stimulation in five and left carotid stimulation in seven. There was one example of intraventricular conduction disturbance, namely bundle-branch block following left carotid pressure.

By far the most common type of response to both right and left carotid stimulation was sino-auricular slowing. A measurable amount of slowing as judged by P–P intervals before and after stimulation was observed 76 times in 49 individuals (73.13 per cent). Right and left sided stimulation were each responsible for 38 instances of slowing. However, in many of these individuals the amount of slowing was slight and may have been due to factors other than the mechanical stimulation of the carotid sinus by digital pressure. In 27 of the 49 individuals the degree of slowing was considerable and we attributed it to compression of the carotid and so tabulated it in determining the general incidence of response.

We shall next consider the total incidence of effective response to carotid sinus stimulation. Previous reports based principally upon blood pressure and pulse rate changes have shown a high percentage of response, varying from about 60 to 80 per cent. This figure is greatly influenced by a number of factors such as age, sex and blood pressure level. In view of the fact that we are here studying only the cardio-inhibitory aspect of the carotid sinus reflex we cannot assume that the reflex was inactive in all who show negative results here. In the present study definite electrocardiographic changes were induced by carotid pressure in 28 individuals or 41.79 per cent of the total of 67. In most instances in which a response was obtained it was observed after both right and left sided stimulation. There were 24 responses to right carotid pressure and 20 responses to left sided pressure. Males as usual showed a greater incidence of response with definite effects apparent in 14 (70 per cent) of the 20 males tested. On the other hand, only 14 (29.78 per cent) of the 47 females showed a response. We must recall here, however, that 21 of these 47 females were student nurses and therefore much younger as a group than the males. Average age of males was 49.95 years and average of females 34.91 years. If we consider the incidence of response in relation to age alone we find a very striking difference between individuals under 40 years of age and those over 40 years of age. In the former group there were 34 individuals, only five (17.85 per cent) of whom gave a response to carotid sinus stimulation. There were 33 in the older age group and 23 or 82.14 per cent showed a response.

It has previously been observed that the incidence of response to carotid sinus stimulation is increased in the presence of hypertension. If we consider levels of 150 systolic and 90 diastolic as upper limits of normal blood pressure we find that only 14 (29.78 per cent) of the 47 with normal pressure responded whereas of the 20 hypertensive individuals there were responses in 14 or 70 per cent. Again, if we consider only the hypertensive group it is found that seven of the eight males in this group gave a response, that is to say 87.5 per cent as opposed to a response in seven or 58.33 per cent of the 12 females in the hypertensive group. The present group of 67 individuals is too small for us to attach any particular importance to the incidence of response in relation to the disease present. We will, however, list the diagnoses and the number of responses obtained in each.

No disease	21	response 3
Hypertensive and arteriosclerotic heart disease	20	response 14
Cardiac neuroses	4	response 1
Syphilis of heart	1	response 1
Rheumatic heart disease	3	response 1
Congenital heart disease	2	response 0
Miscellaneous	16	response 8

This tabulation does serve to indicate the great frequency of response in the presence of hypertension and arterial disease.

Discussion

The general nature of the electrocardiographic changes induced by carotid pressure in this study bear our previous observations to the effect that carotid sinus stimulation may cause either inhibition of impulse formation in the heart or delay in its transmission through the conduction system. These are features which from experimental and clinical study indicate vagus nerve function. The group of patients here studied is not sufficiently large to indicate a definite difference, if any exists, between right and left sided stimulation. Furthermore it is not strictly correct to suppose that the right and left sinus reflex is comparable to direct stimulation of the vagus nerve. It does, however, appear probable that the reflex on each side is predominantly, at least, manifest through the homolateral vagus and that, just as in the case of animal experimentation with direct stimulation of the vagi, right sided stimulation seems to have a greater influence upon impulse formation in the sino-auricular node and left sided stimulation a greater effect upon auriculo-ventricular conduction and ventricular response. This is suggested by the fact that inhibition of the auricles was twice as common following right carotid pressure, changes in amplitude of the P-wave were nine to seven more frequent after right sided stimulation and the one instance of inversion of the P-wave followed the right sided reflex. On the other hand, there was a seven to five predominance of left sided stimulation in causing prolonged P–R interval, there was a two to one predominance of the left side in causing inhibition of the ventricles and the single instance of intraventricular conduction defect followed the left sided reflex.

The relatively high incidence of profound changes in the cardiac mechanism following carotid sinus stimulation in a group of individuals who had clinically normal carotid sinus reflexes emphasizes the possibility that an overactivity of this reflex may be responsible for syncopal seizures as well as cardiac abnormalities.

The results of the present study coincide with those of previous studies in respect to the influence of age, sex and blood pressure upon the frequency of response to mechanical stimulation of the carotid sinus. Females react less well than males, and the response increases with age and elevation of blood pressure. There has been much discussion in the literature with regard to the causes of overactivity of the carotid sinus reflex. Weiss and Baker [9] state that it is due to one of three factors: (1) excitability of the afferent nerve endings within the sinus, (2) the state of the medullary centers, or (3) excitability of the efferent cardiovascular nerve endings. Sigler [10] says that all factors point to a constitutional vagotonic tendency. No doubt there are many factors which influence the activity of the reflex, but it appears that the effect of one very obvious factor has received too little attention. This factor proved of importance in this study, and will likewise be of importance in any study of the carotid sinus reflex in which the means of inducing the reflex is compression of the carotid artery distal to the sinus. It is vastly easier to locate and properly compress a carotid artery if that vessel is hardened by arteriosclerosis or distended by hypertension than it is to properly compress a vessel which presents a poor pulsation and is therefore difficult to locate. Previous reports have all left the impression that the actual degree of irritability of the carotid sinus reflex itself was determined by the response obtained from pressure in the neck although a strong response to such "mechanical stimulation" does not of necessity prove an inherent greater tendency to respond, that is to say, nerve irritability, but may be due to a more efficient application of the stimulus in those cases in which the artery is sclerotic or hypertensive. This fact could account for the greater incidence of response in the older age groups and will explain partly, at least, the greater incidence of response in males, for they more often show a hypertension or arteriosclerosis than do females. It must be constantly considered if, as suggested by Weiss and associates, we are to use the carotid sinus reflex as a basis for judging some of the functions of the autonomic nerve system. Also in studying the effect of various drugs in sensitizing or desensitizing the carotid sinus reflex we must remember that in some individuals we may be able to apply more efficient stimulation than in others by reason of changes in the carotid vessel or other structure in the neck. Occasionally the presence of hardened lymph nodes makes mechanical stimulation of the reflex more perfect. It would appear, therefore, that the term "hypersensitivity of the carotid sinus reflex" as applied to those cases that have syncopal seizures might more appropriately be "overactivity or hyperactivity of the carotid sinus reflex" except in those instances in which it may be possible to prove the increased irritability of the

reflex by some means other than mechanical stimulation by pressure in the neck.

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SUBACUTE BACTERIAL ENDOCARDITIS DUE TO STREPTOCOCCUS VIRIDANS WITH SPECIAL REFERENCE TO PROGNOSIS *

By Joseph A. Capps, M.D., F.A.C.P., *Chicago, Illinois*

Introduction

In the year 1910 a young man came under my care at St. Luke's Hospital, complaining of daily fever, night sweats, and exhaustion. During the next few days petechiae appeared in crops on the skin, the spleen became palpable, and red blood cells were found in the urine. The presence of a loud systolic murmur over the apex of the heart prompted recourse to blood cultures, whereupon Dr. Rosenow in two attempts succeeded in obtaining an abundant growth of *Streptococcus viridans*. For lack of any specific treatment, this patient was given intravenous injections of sodium cacodylate daily for 12 weeks and was kept in bed. For the first month the fever, petechiae, and hematuria continued without change. During the second month all the symptoms improved. By the end of the third month, the fever was almost normal, embolic signs had disappeared, and the patient was regaining weight and strength. For a year thereafter he led a quiet life, then resumed his business. Today he is in good health, although the heart murmur persists. Because of the unexpected outcome of this case, I decided to make a follow-up study of patients with bacterial endocarditis.

Since then I have attempted to learn the end results of all the patients with *Streptococcus viridans* subacute bacterial endocarditis coming under my observation in private practice and in Cook County and St. Luke's Hospitals. It has been impossible to keep track of most of the Cook County patients after their discharge from the hospital and also a considerable number seen elsewhere.

This paper represents a study of 139 cases of subacute bacterial endocarditis, all followed to the time of death or over a long period of years up to 1937 or 1938.

Realizing that the reliability of blood cultures depends to a degree on skill and experience, practically all cultures were originally made or confirmed by St. Luke's Laboratory.†

By way of introduction, it may be profitable to pass in review the successive milestones marking the progress of our knowledge of bacterial endocarditis from its earliest discovery to our present-day conceptions.

1. *Earliest Recognition.* One of the first descriptions of ulcerative endocarditis was that of Rokitansky [1] in 1855. He described "fibrinous

* Read at the New Orleans Meeting of the American College of Physicians, March 27, 1939.

† I am indebted to the Borland Fellows of St. Luke's Hospital, especially to Drs. Bargen and Biggs, for their contribution to this study, and to the laboratory directors, Drs. Davis, Dick, and Hirsch.

vegetations on the bicuspid valves in the heart of pneumonia, round and sausage-shaped formations of stiff, hyaline, albuminous matter, enclosing a multitude of small granules, which shrink under the influence of acetic acid." This is one of the earliest descriptions of bacteria in endocarditis. Pasteur [2] states that as early as 1860 he had seen organisms in chains.

To Virchow,[3] 1856, belongs the credit for revealing the relationship of ulcerative endocarditis to infarcts in various parts of the body. Upon these observations Virchow built up his theory of embolism which is rated by pathologists as perhaps his greatest single achievement. He also noticed minute glistening bodies in the endocardial exudate and suggested that if the granules could be brought into etiologic relationship to the endocarditis, the whole process might be explained.

2. *Discovery of Bacteria in Valvular Vegetations.* The conclusive evidence demanded by Virchow was offered by Winge [4] and Heiberg [5] in 1869 according to Hektoen.[6] They demonstrated a heart with "large grayish vegetations on the aortic and tricuspid valves, with ulceration." They found infarctions in the lungs and kidneys. In the endocardial vegetations were "leptothrix chains which were striated like a rosary or string of beads." Probably this is the first convincing description of streptococci in endocardial vegetations.

The association of bacteria with ulcerative endocarditis was further confirmed by Klebs,[7] 1878, and Köster,[8] 1886.

3. *Experimental Reproduction of Bacterial Endocarditis in Animals.* At this period the theory of bacterial infection was rapidly gaining adherents, and the influence of Koch was demanding more rigid methods for the proof of this conception.

The experimental method was being introduced, and some investigators turned their attention to the inoculation of animals with pure cultures of the bacteria grown from the ulcerative vegetations of endocarditis. Wyssokowitsch,[9] 1885, occasionally succeeded in producing endocarditis in rabbits in this manner, and he found that more certain results were achieved if the heart valves were previously wounded. Later Rosenow [10] and Kinsella [11] perfected the technic to such a degree that they reproduced the endocarditis with ease. Rosenow discovered that the first infections of cocci rarely caused endocarditis, but rendered the animal more susceptible to later inoculations.

4. *Classification of Bacteria.* With the turn of the century, bacteriological studies of the organisms found in the vegetations and in the blood greatly enriched our knowledge of the disease.

It was soon recognized that there were two types of bacterial endocarditis—a primary endocarditis in which the portal of entry was unknown or obscure, and a secondary form of endocarditis in which there was a known source of infection pouring bacteria into the blood stream and producing endocarditis as a part of a general septicemia.

Sittmann,[12] Lenhartz,[13] and Cannon [14] were pioneers in establishing the value of blood cultures. Lenhartz named the bacteria of ulcerative endocarditis parvus; Schottmüller [15] originated the term *Streptococcus mitior* or *viridans;* Horder [16] called this organism *Streptococcus saprophyticus;* Libman,[17] endocarditis coccus; and Rosenow, a modified pneumococcus. It was later agreed that these were all essentially the same organism, and the term *Streptococcus viridans* was adopted. Other organisms such as the influenza bacillus, pneumococcus, gonococcus, and staphylococcus may be responsible for subacute bacterial endocarditis, but it is the experience of Libman and others that about 95 per cent of all patients with this disease are infected by *Streptococcus viridans.*

5. *Clinical.* Just as in the demonstration of the importance of coronary thrombosis the pathologist showed the way and the clinician slowly learned to diagnose the condition, so in ulcerative endocarditis the pathologist blazed the trail which the clinician followed step by step.

Osler [18] in 1885 first called attention to the acute cases of septic endocarditis and in 1908 he gave a clear description of 10 cases of chronic infectious endocarditis, all with fatal termination. The daily remittent fever, the petechiae, the painful nodes under the skin, the occurrence of emboli in the brain, kidneys, and retina were all noted.

Osler's publication was soon followed by Billings' [19] report of 14 cases of chronic infectious endocarditis, the notable feature of his contribution being the successful blood cultures in every patient—an achievement made possible by repeated efforts and improved technic. In 11 cases Rosenow isolated the "modified pneumococcus," and in three the *Streptococcus viridans.*

Libman then entered the field, and by his extensive pathological, bacteriological, and clinical studies has been a leader in the advancement of our knowledge of the disease.

6. *Healing of Valves.* The first ray of hope for victims of this deadly malady came from Harbitz,[20] 1899, and Bartel,[21] 1901, both of whom expressed their conviction that in the hearts of persons dead from chronic infectious endocarditis some of the lesions were in the "healing" stage and free from bacteria.

In 1912 Libman recorded 11 postmortem cases which showed characteristic lesions of bacterial endocarditis and which during life yielded negative blood cultures. In some instances he could differentiate three stages of the process in valvular vegetations—active bacterial, bacteria-free and healing, and bacteria-free and entirely healed. Clinically the patient with healing valves may develop nephritis or cardiac decompensation, or present a picture similar to that of the patient with bacteremia, i.e., fever, emboli.

Since then LeCount,[22] Jaffe,[23] and many other pathologists have borne testimony to the presence of healed lesions in bacterial endocarditis—scarring and calcification with disappearance of bacteria. Hamman [24] has

recently emphasized the marked evidence of healing frequently encountered in necropsies.

7. Clinical Recoveries. Looking back to this period, it seems surprising that with all the postmortem evidence of healing and healed bacterial endocarditis so little mention was made of clinical recovery. As a matter of fact, the earlier reports of recovery were looked upon with general skepticism.

However, there appears here and there in the literature an isolated report of recovery. Many of these published cases presented unsatisfactory proof of a correct diagnosis; still others, with an adequate clinical history and blood cultures, had survived so short a time that the appearance of recovery might well be interpreted as a remission which so often occurs in this disease.

In the accompanying table (table 1) some of the more authentic cases are cited, along with the treatment administered and the duration of the recovery period.

TABLE I

Reported Recoveries of One Year or More

Author	Year	No. Cases	Treatment	Length of Recovery Period
Latham and Hunt	1910	1	Vaccine	1 year
Oille, Graham and Detweiler	1915	23	Seven with vaccine; others —no therapy	10 years later all living
Lorey	1917	1	Salvarsan	1 year
Salus	1920	18	Not stated	Not stated
Capps	1923	4	Sodium cacodylate	Over 2 years
Hess	1925	1	Kollargol	4 years
Howard	1926	1	No specific therapy	4½ years
Kissling	1935	1	Immuno-transfusion	4 years
Libman	1935	12	No specific therapy	From 3 to 20 years
Kraiss	1936	1	Normal serum	2 years
Horder	1936	2	One with radium; one—immuno-transfusion	18 months to 20 years
Chester	1937	1	No specific therapy	3½ years
Palowe	1939	1	Splenectomy	20 months

There appear in the literature two reports of what might be termed epidemics of subacute bacterial endocarditis.

Salus,[28] 1920, describes a group of 18 cases with *Streptococcus viridans* bacteremia, all of notably mild nature, with low fever and leukopenia. At the end of 12 to 18 months most of the patients were living. The scant details presented by the author, however, seriously impair the validity of the diagnosis.

More significant is the report of Oille, Graham, and Detweiler,[26] 1915 to 1925. These authors discovered, during a three-year period, a group of 23 persons suffering from mild symptoms of anemia, arthritis, neurasthenia, with little or no fever. All exhibited heart murmurs, and all yielded positive blood cultures of *Streptococcus viridans.* A follow-up report 10 years later revealed that all were living. Because of the reliability of these investiga-

tors, this report stands out conspicuously as the only verified instance of an epidemic of mild or benign subacute bacterial endocarditis.

Thayer [37] reports one recovery of unstated duration; he also refers to one case of recovery by Keefer after 7 months, and one by Stengel of unstated duration. Billings had one case of recovery over four years that was never published.

Criteria of Diagnosis

The criteria upon which the diagnosis of subacute bacterial endocarditis is based have been so fully discussed by Coler, Thayer, Blumer,[38] and others that it is unnecessary to review in detail all the symptoms and clinical findings of the disease.

At the present time we must depend upon:

1. The signs of an active endocarditis.
2. Fever, often of low grade.
3. Positive blood cultures, revealing either streptococcus, pneumococcus, gonococcus, influenza bacillus, or rarely staphylococcus.
4. Embolic phenomena, viz., petechiae in the skin, red cells or albumin in the urine, enlargement of the spleen, or local symptoms from lodgment of bacteria in the brain, the lungs, or the extremities.

Of all these findings, the heart murmurs and fever are the most constant. Embolic signs may come and go, but without successful blood cultures one cannot be sure of the diagnosis.

We know, however, that many mild cases of subacute bacterial endocarditis escape recognition because of negative blood cultures.

Recently Weiss and Rhoades [39] have called attention to a case in which typical necropsy evidence of healed bacterial endocarditis was encountered and whose clinical history and examination had revealed no suggestion of the disease.

Incidence of Subacute Bacterial Endocarditis over Long Periods

The variability of the incidence of this disease year after year is comparable to that seen in other infections.

In the accompanying chart (chart 1) covering the period from 1910 to 1937, I should like to call attention to several deductions:

1. There were very few cases observed in the period from 1910 to 1920.
2. There was an abrupt rise in the number of cases in 1922 (12 cases); a peak in 1923 (22 cases); a fall in 1924 to 13 cases; and an irregular number from 1925 to 1937.
3. The average number of cases from 1922 to 1937 is much greater than in the period from 1910 to 1922.

It is of interest to compare with our series the incidence of subacute bacterial endocarditis in the Massachusetts General Hospital during the period

from 1910 to 1926. From 1910 to 1921 there occurred two to eight cases per annum; in 1922 the number increased to nine; in 1923, to 16; in 1924 it fell to eight; in 1925, to 14; and in 1926 it was down again to seven cases.

The Boston epidemic wave took place in the years 1922, 1923, 1924, and 1925, as compared with the Chicago wave in the years 1922, 1923, and 1924. Morrison [40] published at the same time the incidence of rheumatic fever at the same hospital and concluded that it bore no relationship whatever to the incidence of subacute bacterial endocarditis.

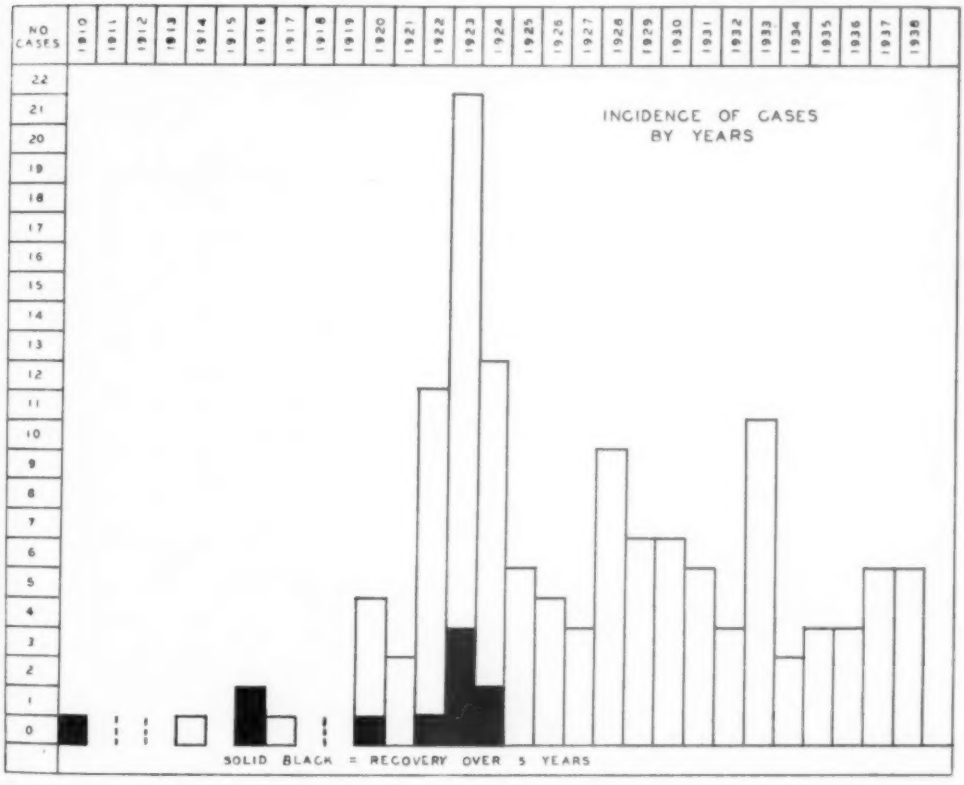

CHART I

4. The recovered cases were observed in the following sequence:

One in 1910.
Two in 1916.
One in 1920.
One in 1922.
Four in 1923.
Two in 1924.

Eight of the 11 cases of recovery occurred in the period from 1920 to 1924.

It has been my misfortune to have seen no instance of recovery since 1924.

Arrested or Recovered?

Is the term recovery justified with respect to this disease?

We may profitably compare this infection to pulmonary tuberculosis which is so subject to phases of healing and exacerbation. In tuberculosis the term "arrested" is continually used to designate "improvement." The word "recovered" is reserved for those cases that have gone many years without symptoms.

Likewise, with bacterial endocarditis, we might properly employ the term "arrested" for the cases that are symptom-free. However, a considerable number of patients who become apparently well for months, or even a year or two, undergo a relapse with fresh bacteremia.

In our series of 139 cases there is a group of 10 patients who survived the initial attack one to two years—"arrested cases." Six of this group died from a relapse of the heart infection; four died of cardiac decompensation and nephritis. It has been shown by Baehr that glomerular nephritis is a characteristic sequel of bacterial endocarditis in the bacteria-free stage. Therefore, it might be said that these four nephritic patients died, not from the infection itself, but from its complications.

To avoid any controversy, we have included in this series of recoveries only those patients who have remained symptom-free for a period of over five years.

Author's Cases with Recovery of Five Years or More

Eleven patients were living from eight to 26 years after the attack of endocarditis.

Clinically these recovered cases differed from the fatal cases in several respects. Six of the 11 cases were office patients; whereas, the great majority of the fatal cases were confined to bed when first observed.

These patients, with one exception, were not very ill, complaining of weakness, a low daily fever, loss of appetite, palpitation, night sweats, and exhaustion. At first they were suspected of having lymphadenitis, tuberculosis, thyrotoxicosis, or visceral lues, until the appearance of heart murmurs, embolic signs, enlargement of spleen, and positive blood cultures cleared up the diagnosis.

It is noteworthy that seven of the 11 recovered cases occurred in the years 1923 and 1924, corresponding to the peak incidence of all cases.

The only follow-up report of bacterial endocarditis comparable to this series is that of Libman, who describes the recovery of 12 patients for periods ranging from three to 20 years.

A curious circumstance is that nine of Libman's recoveries occurred in the period from 1921 to 1924—the same period in which the majority of

TABLE II

TABLE II

Cases Recovered over Five Years

Name	Date	Period of Observation	Previous Duration	Previous Rheumatism	Valves Affected	Temperature	Emboli				Blood Cultures	Treatment Sod. Cacod.	Outcome
							Spleen	Kidney	Skin	Elsewhere			
1	1910	26 years	1 month	0	M	101 to 102	++	Alb. Rbc.	Petechiae	0	Strep. vir. Twice	10 weeks	Living (1936)
2	1916	19 years	4 months	+	M	97 to 100	0	0	0	0	Strep. vir. Once	4 months	Living (1935)
3	1916	14 years	1 year	0	M-A	99 to 100	+	Alb. Rbc.	Petechiae	0	Strep. vir. Once	9 weeks	Died (1930) Decomp. and Neph.
4	1920	8 years	2 months	+	M	98 to 101	0	Alb. Rbc.	0	0	Strep. vir. Twice	13 weeks	Living (1928)
5	1922	11 years	2 months	+	M	99 to 100.5	0	0	Petechiae	0	Strep. vir. Twice	3 months	Living (1933)
6	1923	14 years	18 months	0	M	97 to 100	0	Alb. Rbc.	0	0	Strep. vir. Twice	3 months	Living (1937)
7	1923	8 years	6 months	+	M	99 to 99.5	0	0	0	0	Strep. vir. Once	3 months	Died (1931) Heart Decomp.
8	1923	9 years	1 month	+	M	98 to 99.5	0	0	0	0	Strep. vir. Once	4 months	Died (1932) Decomp. and Neph.
9	1923	13 years	6 months	+	M	99 to 100	+	0	0	0	Strep. vir. Twice	10 weeks	Living (1936)
10	1924	13 years	2 weeks	0	M	98 to 100	+	0	0	0	Strep. vir. Once	8 months	Living (1937)
11	1924	12 years	9 months	0	M-A	99 to 100	0	Rbc.	0	0	Strep. vir. Twice	4 months	Living (1936)

our cases were seen. Another startling fact is that he records no recoveries since 1924, nor have we observed any since 1924. What is the significance of this coincidence? May we expect to find these cases in clusters like four-leaf clovers? A partial explanation may be that these years represented the peak wave of all cases and in an epidemic wave we may encounter more mild cases. Or must we assume that the organism goes through cycles of changing virulence?

TABLE III

Cases Surviving 5-Year Period

1 patient survived, 26 years, still living.
1 patient survived, 19 years, still living.
2 patients survived, 14 years, one still living, one died of cardiac decompensation and nephritis.
2 patients survived, 13 years, still living.
1 patient survived, 12 years, still living.
1 patient survived, 11 years, still living.
1 patient survived, 9 years, died of cardiac decompensation and nephritis.
2 patients survived, 8 years, one still living, one died of cardiac decompensation

TABLE OF COMPARISON OF RECOVERED AND FATAL CASES

In table 5 is presented a comparison of the recovered with the fatal cases, in respect to the history and the clinical findings.

TABLE IV

Comparison of Recovered with Fatal Cases

	Recovered Cases	Fatal Cases
Previous rheumatism	54%	68%
Valves affected: Mitral alone	85%	65%
Valves affected: Mitral and aortic	15%	35%
Temperature	99.5° to 101°	101° to 105°
Spleen enlargement	35%	75%
Albuminuria or hematuria	45%	74%
Petechiae	27%	60%
Cerebral embolism	0	20%
Osler's nodes	0	8%

ENTRY OF INFECTION

It is beyond the scope of this paper to enter into all the discussion pertaining to the origin of subacute bacterial endocarditis, but certain facts have been established which may be enumerated briefly:

1. *Streptococcus viridans* commonly inhabits the throat, tonsils, sinuses, teeth, and intestinal tract, and less frequently the gall-bladder, bronchi, urinary bladder, and genital organs.

2. It is probable that the green streptococci, which have a low degree of virulence, on many occasions enter the blood stream and are destroyed without any resulting damage. However, under certain favoring conditions, the organisms may invade the heart valves—either directly through the coronary arterial capillaries, or more likely by direct implantation on the valves.

3. As in animal experimentation, injury of the valve increases susceptibility to infection; so in human beings, a valve previously damaged by

rheumatism or by a congenital deformity becomes more vulnerable to infection.

Prevention

In view of the fact that in a majority of instances the elective location for the invasion of *Streptococcus viridans* is in the site of an old rheumatic endocarditis, our first efforts should be directed to the prevention of rheumatism and rheumatic endocarditis.

We are handicapped in preventing rheumatism because there is no agreement concerning the etiology. However, working on the presumption that it is an infection, valiant efforts have been made to stem the tide of rheumatic fever by eradicating every possible focus of infection that may contaminate the blood stream. So far as may be determined by proved results, the campaign has been thus far disappointing.

More promising are measures proposed for minimizing the damage inflicted on the valves during rheumatic fever, viz., by a prolonged period of rest after the fever has subsided.

It is important to recognize that a patient with an old rheumatic heart valve or a congenital heart lesion is peculiarly vulnerable to *Streptococcus viridans* infection. Therefore, such a person when affected by a respiratory infection should resort to bed rest more promptly and remain in bed a longer time than the average individual.

Treatment and Prognosis

When one peruses the literature of recovered cases and the treatment prescribed, one is impressed with the multiplicity of remedies employed—a circumstance suspicious in itself.

Transfusions of the blood of donors immunized with the patient's organisms have been of doubtful value. Kilgore [41] saw no beneficial effects in three such cases, and in reviewing the reports of Lamb, Howell, Portis, Beverley, Kurtz and White, Wordley, Robinson, and Dick, he concluded that there had been no unequivocal record of success.

Vaccines have failed in extensive tests. Sera of persons immunized against *Streptococcus viridans* have also been of little value, as might be anticipated, since the blood of the victim of subacute bacterial endocarditis is already rich in bactericidal and immune bodies.

Chemotherapy has many votaries: kollargol, mercurochrome, gentian violet, arsphenamine, cacodylate of sodium, and sulphanilamide,—but we cannot pin our faith to any of them. Sulphanilamide has on the whole been disappointing, but it is too early to estimate its value, as several recoveries over short periods have been reported by Hussey [42] and others.

In all our recovered patients, as well as in most of the fatal ones, sodium cacodylate was given intravenously, three grains a day, over a period of six weeks to three or four months. It is practically non-toxic because of its

rapid elimination. Recent investigations on the action of arsenicals on the spirochete of syphilis and of relapsing fever seem to demonstrate that the chief action of the drug (arsphenamine) is not bactericidal, but that it exerts a powerful stimulus on the reticulo-endothelial system resulting in increased phagocytosis and in the production of immune substances. Therefore, it is conceivable that cacodylate may have some value in this direction.

The most important therapeutic measure, in our opinion, is prolonged bed rest. Many of our recovered patients were ambulatory—not well enough to work, but not ill enough to remain in bed voluntarily. Regardless of their inclination, after the diagnosis was established, these patients were put to bed and kept there for not less than two months, more often for three or four months. Following this rest period, the patient was allowed to exercise very little. The treatment was similar to that recognized as advisable in early febrile tuberculosis of the lung.

To what extent the cacodylate of soda treatment contributed to recovery, it is impossible to say, but probably the drug played a minor rôle.

Do rest and chemotherapy have any value in the ordinary septic case with high fever and numerous embolic phenomena? Very rarely do such patients recover.

Our only hope of a successful outcome is that we may be fortunate in suspecting the condition in certain ambulatory patients who have a low fever of "undetermined origin" and in whom the presence of a heart murmur prompts us to take repeated blood cultures that show colonies of *Streptococcus viridans*. It is in the office and the dispensary, not in the hospital wards, that we will usually discover the mild cases which have some chance of recovery.

I think the time has come for us to change our conventional outlook on this disease. May I again revert to the analogy of coronary thrombosis. For many years the pathologists knew that coronary thrombosis was a common cause of sudden death. At this early period clinicians considered that coronary infarct was nearly always fatal. It was not until Herrick [43] taught us how to make the diagnosis during life that we learned that many patients with coronary occlusion survived the attack and even lived many years afterward. Now in the treatment of coronary thrombosis, it is not certain that any remedies materially affect the prognosis, but thanks to early recognition of the infarct the patient is kept in bed over a long period and it is probable that this measure saves a good many lives.

In similar fashion our conception of the prognosis of subacute bacterial endocarditis may change. We have become so familiar with the septic type of the disease, which has nearly always a fatal outcome, that we have overlooked another group of patients with a mild degree of infection in which there is a chance of recovery.

Summary

1. The development of our knowledge of subacute bacterial endocarditis is reviewed. The early recognition of ulcerative endocarditis, as distinct from other forms, was followed by the detection of streptococci in the vegetations. Further studies established the disease as a clinical entity, and blood cultures made possible a classification of the exciting organisms. Pathologists later on described the evidence of healing in the valves before clinical recoveries were reported. In most cases *Streptococcus viridans* is the guilty organism.

2. The more authentic instances of recovery in the literature are cited.

3. The author reports a follow-up of 139 cases of subacute bacterial endocarditis due to *Streptococcus viridans*. These cases were seen in private and hospital practice over a period of 28 years. In all patients there were heart murmurs, fever, blood cultures yielding *Streptococcus viridans,* and often embolic phenomena.

4. A chart recording the occurrence of cases over the period 1910 to 1939 shows a remarkable rise in the incidence of the disease in 1922, a peak in 1923, a recession in 1924, and a smaller average number in succeeding years.

5. The author describes 11 cases of subacute bacterial endocarditis who survived more than five years after the onset of the infection. Eight of these cases occurred in the period 1920 to 1924 when the incidence of the disease was highest.

6. A comparison of the recovered with the fatal cases shows that in the recovered group the fever on the average was lower and embolic phenomena less in evidence. None developed cerebral emboli or Osler's nodes.

7. Clinically the recovered patients with a few exceptions were up and around (complaining of fatigue, palpitation, sweating, loss of appetite, and loss of weight). As a rule they did not seem very ill—in marked contrast to the septic appearance of most of the fatal bed patients. Examination revealed a daily temperature usually around 99° F. to 100.5° F., heart murmurs, and often red cells in the urine, or a palpable spleen. The diagnosis was not determined, however, until blood cultures, often repeated, grew colonies of *Streptococcus viridans.*

8. Treatment of the author's cases consisted primarily of prolonged bed rest of two to four months; also, as a routine, cacodylate of soda was injected intravenously every day for six to 12 weeks. The rest is all important. The value of the arsenic cannot be determined, but at best it plays a secondary rôle.

9. The prospect, with our present knowledge, for improving the chances of recovery in subacute bacterial endocarditis lies, not in treatment of the severe septic cases, but in the early recognition of mild cases and the immediate and prolonged enforcement of bed rest.

10. Finally, it is suggested that a more open-minded attitude may encourage us to investigate more systematically the patients with unexplained

fever and heart murmurs with the hope that early diagnosis and proper treatment will sometimes help nature to arrest the disease.

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THE RÔLE OF THE UPPER SMALL INTESTINE IN THE CONTROL OF GASTRIC SECRETION; THE EFFECT OF NEUTRAL FAT, FATTY ACID, AND SOAPS; THE PHASE OF GASTRIC SECRETION INFLUENCED AND THE RELATIVE IMPORTANCE OF THE PSYCHIC AND CHEMICAL PHASES *

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THE prohibition in Leviticus †: "Ye shall eat no manner of fat, of ox, or of sheep, or of goat," might mean that the ancients were aware of the retardation of gastric digestion by fats. Certainly Aristotle, in his Problemata,‡ discussed the effect of fat upon digestion in the stomach with an assurance that indicated much observation and thought.

In 1886 Ewald and Boas [1] demonstrated that fat in the upper digestive tract decreased gastric activity. Beaumont,[2] too, had previously stressed the difficulty of digestion of oily foods. From Pavlov's laboratory, however, came the first experiments proving that fat diminished gastric secretion. Khigine,[3] who worked on Pavlov pouch dogs, saw a delayed and diminished secretion in the pouch following the introduction of fat into the main stomach. He failed, however, to investigate the mechanism of this action. A short time later Lobassoff [4] studied the problem more fully and concluded that fats mixed with meat produced a gastric juice less in quantity and digestive power than that evoked by meat alone. He believed that this action represented a local gastric effect through special nerve endings.

Le Conte [5] in 1901, after injecting milk into the duodenum of Pavlov pouch and duodenal fistula dogs, observed an inhibition of gastric secretion. Three years later Sokolov [6] almost arrested secretion in the pouch and diminished it greatly in the main stomach of Pavlov pouch dogs by the duodenal instillation of 50 c.c. of cream. Lonnqvist [7] in 1906 clearly stated the nature of the mechanism. From studies in the dog, he showed that fat introduced into the stomach and excluded from the intestines exerted no influence upon glandular activity. However, fat instilled directly into the duodenum was followed by a marked suppression of the quantity and activity of the gastric juice secreted. He concluded succinctly: "Fat inhibits gastric secretion.

* Received for publication October 10, 1938.

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† Leviticus 7: 23.

‡ "How," asks Aristotle, "does the stomach come to digest fat meat slowly?" "Because," he answers, "it swims in the stomach. The best digestion takes place at the bottom of the stomach, where the fat does not descend. Those who eat fat meat are sleepy, because their digestion is hindered."

This inhibition is exerted not from the stomach but reflexly from the intestine." *

More recently a number of investigators have confirmed this intestinal action of fat on dogs. However, except for the investigations of Kauders and Porges [8] and of Roberts,[9, 10] practically no serious attempts have been made to study this problem in man. We have investigated, in considerable detail, the rôle of the upper small intestine in gastric secretion in the human subject.

In this report, we concern ourselves with the effect upon gastric secretion of neutral fat, fatty acid and soap in the upper intestine; the phase of secretion influenced from the intestine; and the relative importance of the psychic and chemical phases of gastric secretion as indicated by our data.

Experimental Method

We selected eight patients with a normal or high gastric acid response to the Ewald meal and with no demonstrable organic gastrointestinal disease. In order to satisfy any questions that might be raised regarding the chemical effect of zweiback and water as the test meal, numerous studies were done with 200 c.c. of a 2 per cent Liebig's extract as the gastric meal. The change in gastric secretion produced by duodenal stimulation was independent of the type of mouth meal used. After an overnight fast, the stomach was intubated with two Rehfuss tubes. One was passed into the duodenum by the usual technic, whereas the other remained in the stomach. When the duodenum was intubated, the positions of the tubes were determined fluoroscopically. The fasting gastric contents were removed and the test meal was administered by mouth. The Ewald meal consisted of 30 grams of zweiback and 300 c.c. of distilled water at body temperature. Duodenal instillation of the test substances in the separate studies was begun with the mouth meal, except when the effect of a time lapse in their administration was being studied.

The effect upon gastric secretion of the additional tube through the pylorus was investigated. We [11] have already reported that a tube so placed did not influence gastric emptying; under similar conditions it failed to modify gastric secretion. These results confirmed like reports by Kauders and Porges.[8] In addition to the duodenal stimulants to be reported here, we studied the effects of hydrochloric acid, organic acids represented by oleic and acetic acid, isotonic and hypertonic solutions of glucose, sodium chloride and sodium bicarbonate, solutions of Liebig's extract, milk and cream, and mineral oil. The duodenal stimulants were instilled from a burette to which a Murphy drip bulb was attached. After the administration of the mouth meal, 15 minute extractions were taken from the stomach in the usual manner for fractional gastric analysis. These extractions were continued in most instances until the stomach was empty.

* "Fett hemmt die Magensecretion. Diese Hemmung wird nicht vom Magen sondern vom Darm reflectorisch ausgelöst."

The gastric specimens recovered were titrated for free and total acid by the accepted technic. Total chlorides were determined by the Wilson [12] modification of the Ball method and pepsin was studied quantitatively by a slight modification of the method of Bloomfield and Polland.[13]

Experimental Data and Discussion

Chart 1 shows the curves for free hydrochloric acid, total acid and total chloride in case D, following the Ewald meal alone. Chart 2 is the response in the same individual when the second tube was through the pylorus. No influence upon gastric secretion resulted from presence of the second tube. However, when olive oil was instilled directly into the duodenum at the rate of 40 drops per minute beginning at the time the mouth meal was taken (chart 4), a very marked suppression of gastric secretion resulted (compare chart 3). Total chlorides as well as free and total acid were greatly depressed. At 105 minutes the intraduodenal drip of oil was stopped and the 15 minute extractions from the stomach were continued. Chart 4 shows that this depression in secretion was continued for another 150 minutes when secretion started to rise sharply until 345 minutes, when gastric evacuation was complete. A similar prolonged effect of fat was noted by Sokolov [6] in his studies in the dog. We have been able repeatedly to duplicate our results. It was interesting to note the almost uniformly depressed level of secretion maintained throughout the test period, giving the impression of a sustained basal secretion by the stomach over which the duodenal mechanism did not appear to have any influence (charts 4, 9). Another feature was the rapid rise in gastric secretion once the inhibited mechanism was freed from the influence of the instilled oil. This rise often equalled the highest levels of secretion seen in the individual. Virschoubski,[14] in 1900, was probably the first to observe this secondary rise in dogs. Orbeli [15] reported instances in his dogs in which the secondary rise of secretion surpassed even the usual normal response for the animal. Feng, Hou and Lim [16] using Bickel pouch dogs also saw an exaggerated response in the third hour after olive oil followed by a meat meal. Similar results were reported by Roberts [10] in human subjects.

The possible explanation for the secondary rise in secretion has intrigued most observers. In 1904 Piontkowski,[17] working in Pavlov's laboratory offered the first explanation for this action. He believed that the secondary rise of the secretion of gastric juice was due to the stimulating effect from the products of fat digestion; namely, the soaps. Babkin [18] confirmed this view, having found active gastric secretion in the empty stomach of a dog 15 to 20 minutes after the introduction of a sodium oleate (concentration not stated) solution through a duodenal fistula. Ivy and McIlvain [19] observed similar effects from the application of a 5 per cent solution of ivory soap to the mucosa of intestinal loops in the dog. Practically all observers have accepted the explanation of Piontkowski [17] and Babkin.[18]

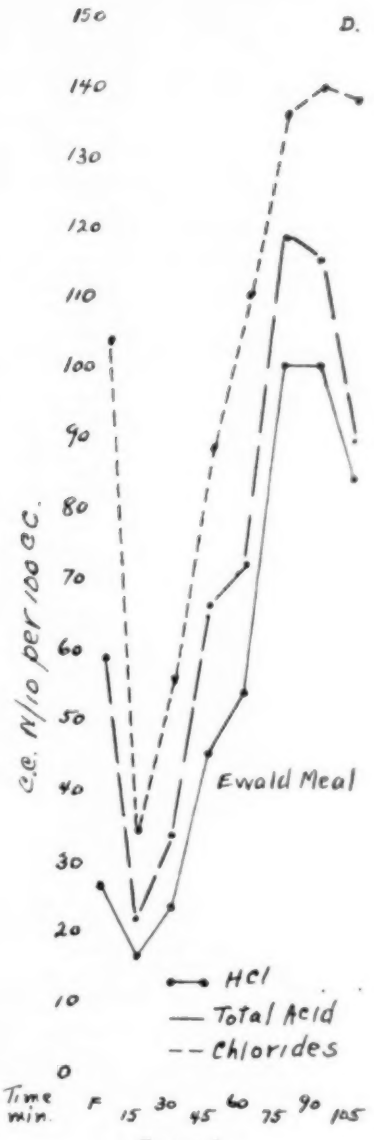

CHART 1.

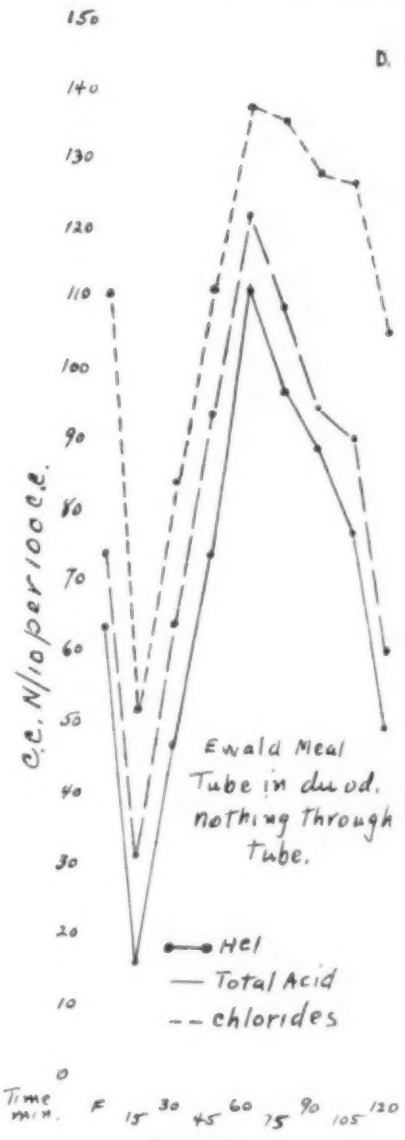

CHART 2.

Patient "D."

CHART 1. Free acid, total acid, and total chloride curve in patient (D) following the test meal alone.

CHART 2. Curves obtained in same patient after similar meal but with a second tube through the pylorus. Note that this second tube did not alter the gastric secretory response to the test meal.

Roberts,[10] although willing to accept their point of view, was not convinced that it was entirely correct. He attempted to clarify the problem by studying the effect upon gastric secretion, after a gruel meal, of the duodenal introduction of an emulsion of linseed oil with sodium oleate. After this procedure, he found a complete suppression of acid secretion for 90 minutes following the gruel meal, followed in turn by a rising curve. His objections to accepting fully Babkin's explanation depended upon the facts:

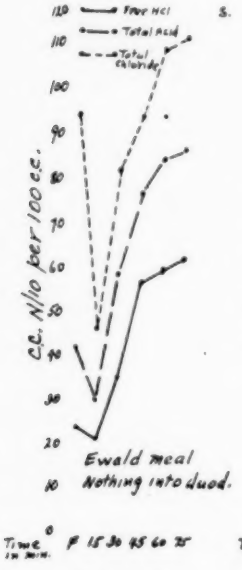

CHART 3.

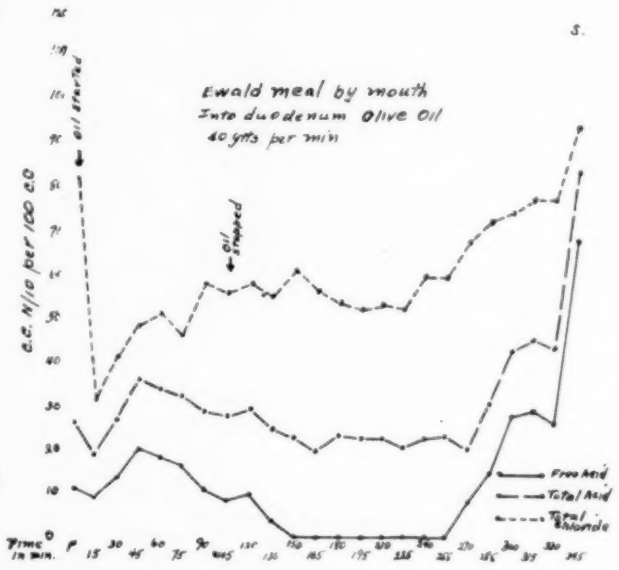

CHART 4.

Patient "S."

CHART 3. Free acid, total acid and total chloride curve in patient (S) following the test meal. The second tube was through the pylorus but nothing was instilled through it at this time.

CHART 4. Conditions same as in chart 3 except that olive oil at the rate of 40 drops per minute was instilled into the duodenum through the second tube. The instillation of the oil was begun when the mouth meal was started, and stopped at 105 minutes later. Note the marked depression in secretion not only of the free and total acid but of the total chloride as well. The depression of secretion was maintained for 150 minutes after the duodenal instillation of the oil was stopped. A sharp rise in gastric secretion then followed which equaled the peak seen in chart 3.

(1) that the amount of oleate normally present in the duodenum during fat digestion must be very small;
(2) that the reported effect of soaps was not observed often enough;
(3) that the inhibitory action of the emulsified oil in his experiments should be seen at once and the supposed oleate effect begin 90 minutes later.

Our own results with sodium oleate solutions justify the misgivings of Roberts [10] and for the human subject at least do not agree with the findings

in the dog of Piontkowski,[17] Babkin,[18] Ivy and McIlvain[19] and others. Chart 5 shows the effect of the duodenal instillation of a 2 per cent solution of sodium oleate. Compared with the result produced with the Ewald meal alone (chart 3), no appreciable effect upon gastric secretion was produced. When, however, the duodenal stimulant was changed to 15 per cent sodium

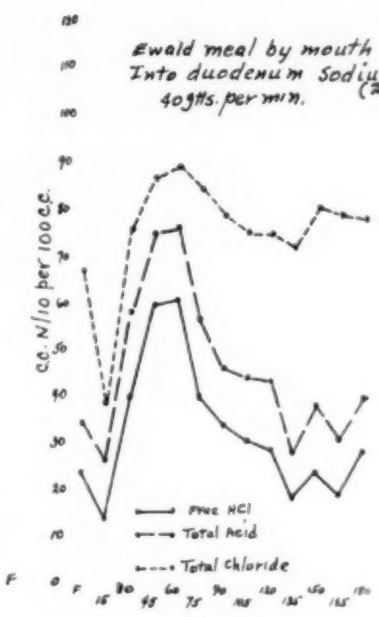

CHART 5.
Instillation of oleate stopped at 105 min.
Patient "S."

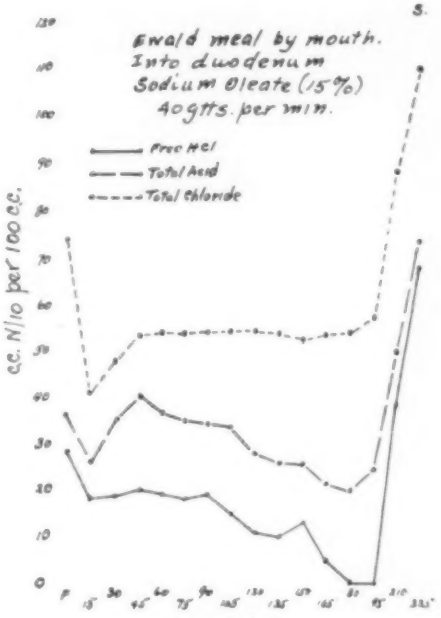

CHART 6.
Instillation of oleate stopped at 105 min.
Patient "S."

CHART 5. Response in patient (S) following the duodenal instillation of a 2 per cent sodium oleate solution under same conditions as in chart 4. Note no appreciable effect on secretion seen as compared with chart 3. However, a very definite delay in gastric emptying resulted. Upon this and chart 6 we postulate a difference in the threshold response of the gastric motor and secretory mechanisms as influenced from the duodenum.

CHART 6. Same as chart 5 except that duodenal instillate was a 15 per cent sodium oleate solution. We now saw a depression of both gastric emptying and secretion, a response entirely comparable in kind to that seen after oil in chart 4. The sharp secondary rise in gastric secretion starting at 195 minutes was also seen. Such results obtained with a soap speaks against the Piontkowski-Babkin explanation that the secondary rise in secretion seen after fat is specifically due to the stimulating effect of soaps formed in the intestine.

oleate, there was a very striking suppression of all the secretory elements (chart 6).

These results permit two rather interesting speculations. First, if we compare the results obtained with the 2 per cent oleate (chart 5) with those of the test meal taken alone (chart 3), we see no appreciable difference in the height of the curves produced, but we do find a very definite delay in gastric emptying in the former. These data indicate that the gastric secretory and motor mechanisms, as influenced from the upper intestine, have

different thresholds of response. The motor mechanism is obviously called into play by a duodenal stimulant milder than the secretory one. However, when the same agent, the oleate solution, is of greater concentration (15 per cent oleate, chart 6) the threshold of response for the secretory mechanism, too, has been passed, which results in secretory, as well as motor, depression. Secondly, the difference between the thresholds of response of the secretory and motor mechanisms, as exemplified in chart 5, probably offers an explanation for the apparent stimulating effect of soaps in dogs reported by

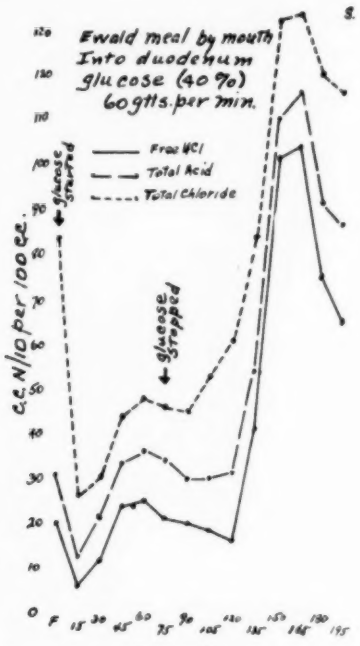

CHART 7.
Patient "S."

CHART 7. Conditions same as in charts 4, 5, and 6, except that duodenal instillate now was a 40 per cent glucose solution. This again showed the depression, followed by the sharp secondary rise in gastric secretion. This rise was most marked after the use of glucose. Such data of course completely negate any specificity to soap as a cause of the secondary rise.

others. If, in their experiments, the soap in the dog's intestine had been of sufficient concentration to inhibit gastric motility but not secretion, such a slowing of gastric emptying could conceivably cause a collection of gastric juice that might falsely indicate an enhanced secretion. Furthermore, chart 6 clearly shows that the action of soap in the intestine in sufficient concentration is identical in kind to that of neutral fat. Finally, any attempt specifically to ascribe the secondary rise in gastric secretion to the presence of soaps in the upper intestine is contradicted by our data obtained with other intestinal stimulants. For present purposes, the results following the duodenal instillation of a hypertonic glucose solution (chart 7) show that no

such specificity exists. Most often, too, the greatest secondary rise in secretion comes after the use of glucose as the intestinal stimulant. We have no explanation to offer for the sharp secondary rise, but we wonder if it might not represent a release of stored up secretion accumulated during the period of depression.

Two factors, other than a specific duodenal mechanism, must be considered to explain the lowered gastric secretion incident to duodenal stimu-

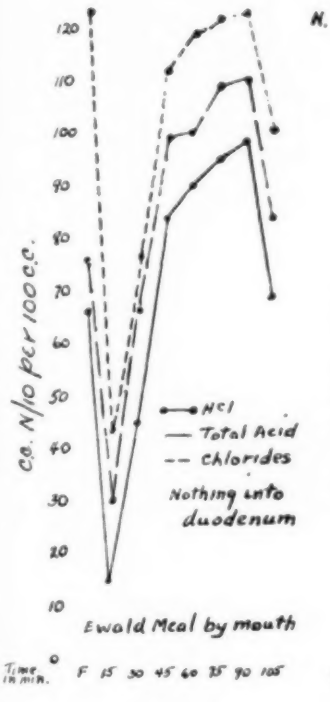

CHART 8.

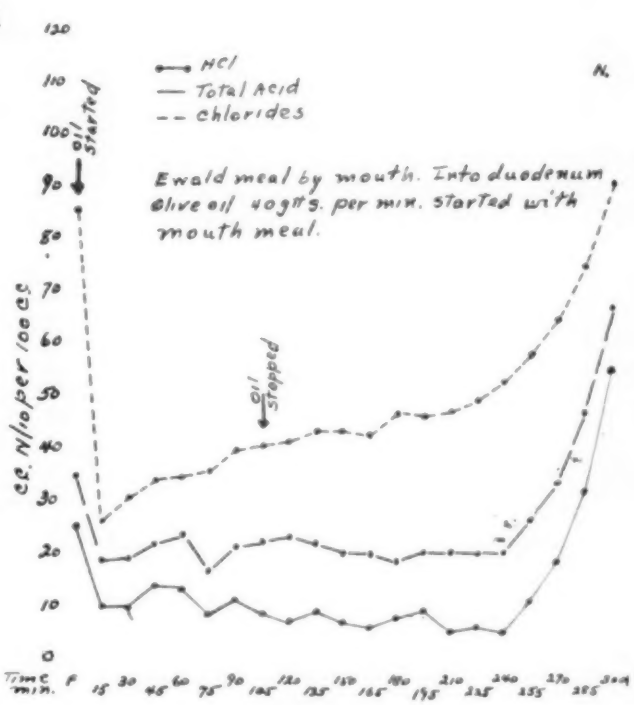

CHART 9.

Patient "N."

CHART 8. Control response to test meal in patient (N).

CHART 9. Response to duodenal instillation of oil in patient N. Conditions same as in chart 4. This chart illustrates very well the question of a basal secretion over which duodenal stimulation appears to have no control.

lation. First, we [11] know from our previous studies on the gastric motor changes from duodenal stimulation, that such stimulation results in delayed gastric emptying. We then have to consider whether the decreased acidity represents merely a dilution of the gastric juice by non-acid diluting fluids from the stomach accumulated incident to the gastric motor delay. Since no reduction in acidity was seen in those instances in which the duodenal stimulant was adequate to produce gastric motor delay without secretory depression, we believe this is not the case.

Secondly, one must consider the possible rôle of duodenal regurgitation in any reduction of gastric acidity in the intact human gastrointestinal tract. Although we [20] have shown that the amount of regurgitation is not sig-

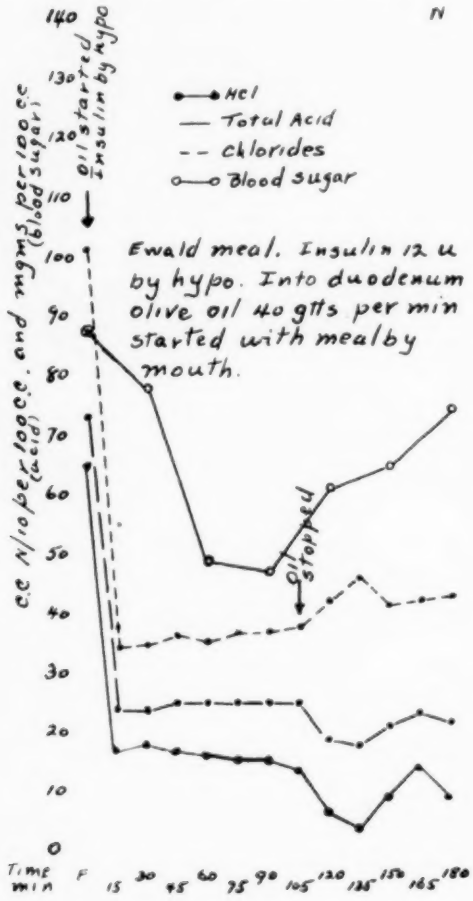
N
Oil started
Insulin by hypo
HCl
Total Acid
Chlorides
Blood Sugar
Ewald meal. Insulin 12 u by hypo. Into duodenum olive oil 40 gtts per min started with meal by mouth.
Oil stopped
cc N/10 per 100 cc. and mgms. per 100 cc (blood sugar)
Time min
F 15 30 45 60 75 90 105 120 135 150 165 180

CHART 10.

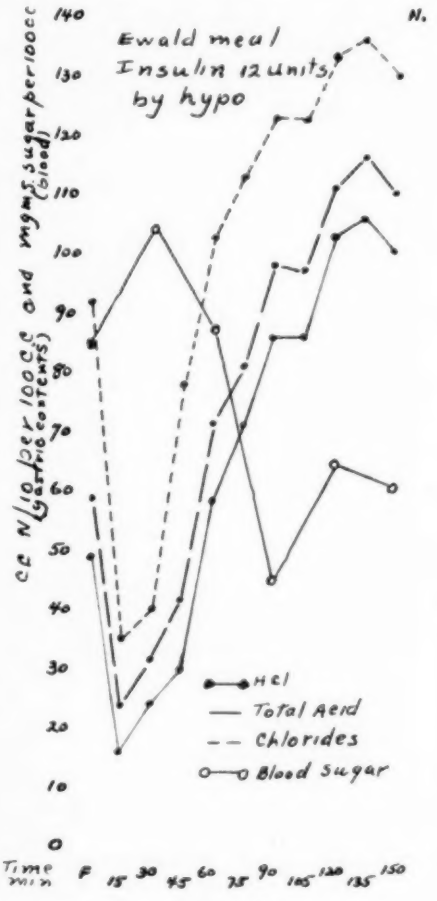
N.
Ewald meal
Insulin 12 units, by hypo
HCl
Total Acid
Chlorides
Blood Sugar
cc N/10 per 100 cc and mgms. sugar per 100 cc (blood) (gastric contents)
Time min
F 15 30 45 60 75 90 105 120 135 150

CHART 11.

Patient "N."

CHART 10. Conditions same as in chart 11, except that the duodenal instillation of olive oil was started with the beginning of the mouth meal. In spite of the fact that a hypoglycemia as marked as that seen in chart 11 was produced, gastric secretion was almost completely suppressed by the oil in the duodenum.

CHART 11. Blood sugar curve and curves of gastric secretion in patient N after test by mouth and 12 units of insulin by hypodermic given at beginning of mouth meal. Note the increased peak of gastric secretion as well as an increased emptying time that accompanied the insulin hypoglycemia (see chart 8). One does not see a striking increase of acidity over chart 8, since we are dealing with a patient who normally has a high secretory response.

nificant in lowering intragastric acidity in the human stomach (findings adequately confirmed by Maclagan [21] in clinical studies, by Teorell [22] in cats, and most convincingly by Hollander [23] in dogs) the idea of duodenal regurgita-

tion as an important mechanism of gastric acid control is still entertained. We assured ourselves that no regurgitation occurred by using bromsulphalein in our duodenal instillate. This dye, recognizable in alkaline solu-

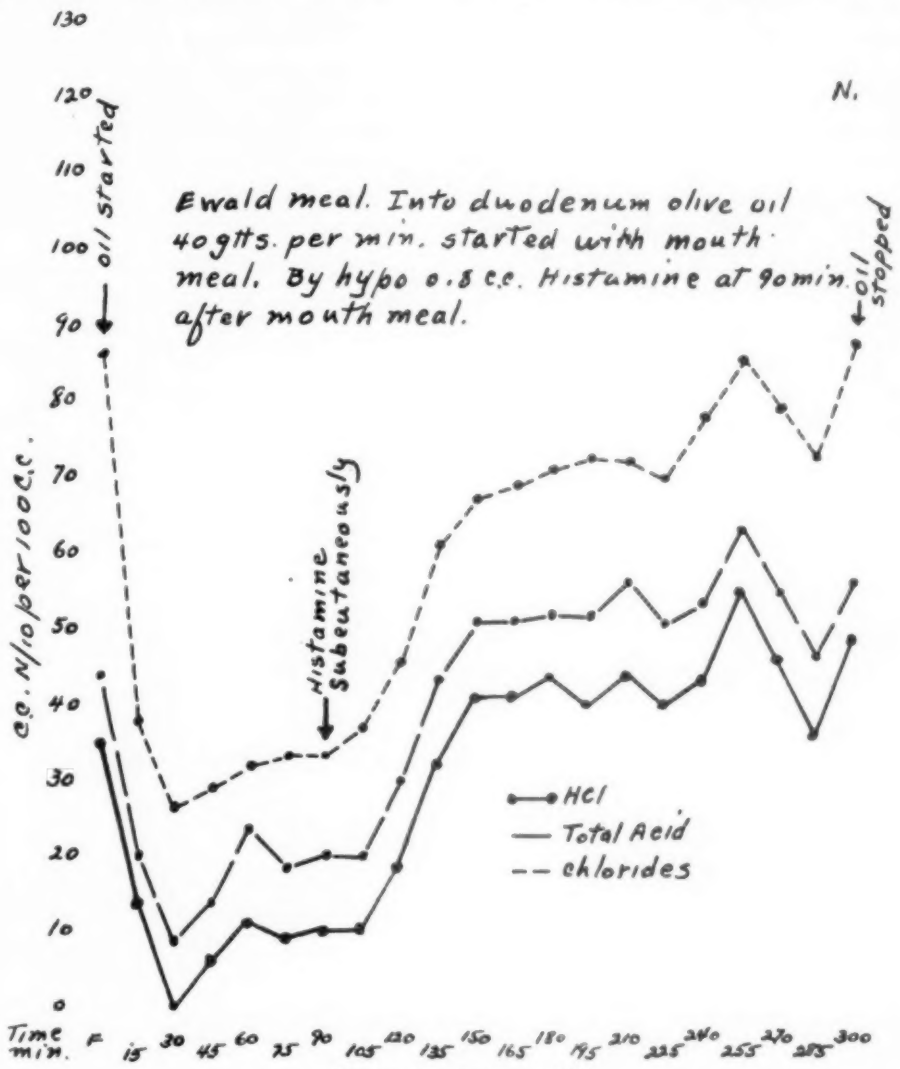

CHART 12. Patient "N."

CHART 12. Olive oil into duodenum started with mouth meal. At 90 minutes when a definite duodenal effect of the oil upon gastric secretion was seen, histamine (0.1 mg. per 10 kilos of body weight) was injected subcutaneously. This was soon followed by a sharp rise in gastric secretion in spite of the fact that the duodenal instillation of the oil was continued for a period of five hours. The results in charts 10 and 12 strengthen the viewpoint that duodenal stimulation influences primarily the cephalic phase of gastric secretion.

tion in one part in a million, was added to the duodenal instillate in amounts approximating 200 milligrams per 100 c.c. A portion of each gastric specimen was made alkaline with 10 per cent sodium hydroxide. Very slight

amounts of duodenal regurgitation could thus be detected easily. Those studies which showed duodenal regurgitation were not included in our data.

We then considered the phase or phases of gastric secretion depressed by duodenal stimulation. Certain of our results led us to believe that the duodenal effect is exerted chiefly, if not entirely, on the psychic phase.

If the rise in gastric secretion incident to the hypoglycemia following insulin injection is dependent upon vagus stimulation, such rise might be considered analogous to that of the psychic phase. Then, if our assumption be correct, duodenal stimulation should prevent the gastric secretory effect of insulin. Charts 8, 10, and 11 show this to be true. In chart 11, we find

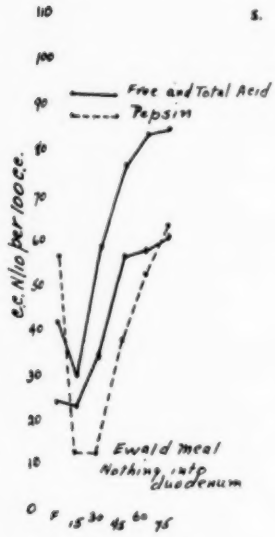

CHART 13.

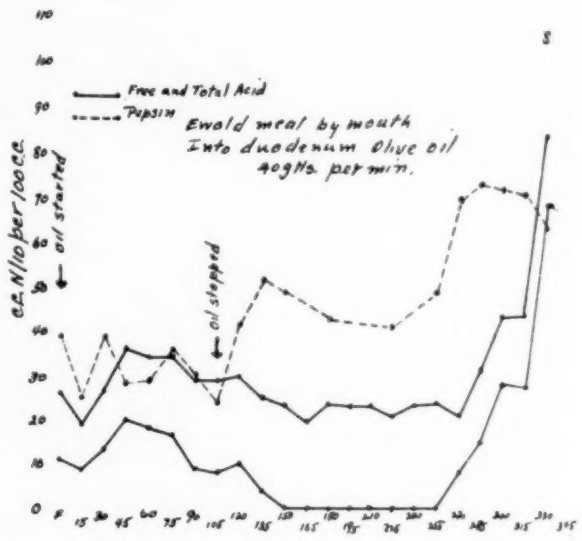

CHART 14.

Patient "S."

CHART 13. Free acid, total acid and pepsin curves in patient S following the test meal.
CHART 14. Same as chart 13 except that olive oil was started into the duodenum with the beginning of the mouth meal. We saw a depression of pepsin concentration as well as that of the other gastric secretory elements. The secondary rise of pepsin secretion appears to take place sooner than does the acid secretion.

the gastric-secretory and blood-sugar curves following twelve units of insulin given at the beginning of the Ewald meal. Chart 10 shows the results following a similar meal and insulin, when the oil was instilled into the duodenum. Although a degree of hypoglycemia similar to that in chart 11 was produced, gastric secretion was maintained only at the basal level seen in chart 9.

Histamine, by its direct effect upon the gastric cell, may possibly be considered to simulate in its action the chemical phase of gastric secretion. Again, if our premise that the cephalic phase of gastric secretion is primarily involved is correct, we should be unable to prevent the gastric secretion called

forth by this agent. Chart 12 illustrates the results obtained. The duodenal instillation of the oil was begun with the mouth meal, and its influence upon the gastric secretion was recorded for 90 minutes in order to assure ourselves that the usual effect of the oil was produced. At this point 0.8 mg. of histamine hydrochloride was injected subcutaneously. Fifteen minutes after this injection, a sharp rise in gastric secretion began, in spite of the continued duodenal instillation of the oil. Thus the opposite results obtained after insulin and histamine fortify the opinion that the effect of duodenal stimulation is largely if not entirely upon the psychic phase of gastric

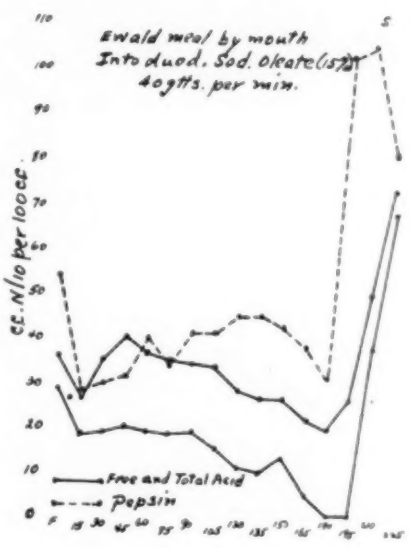

CHART 15.

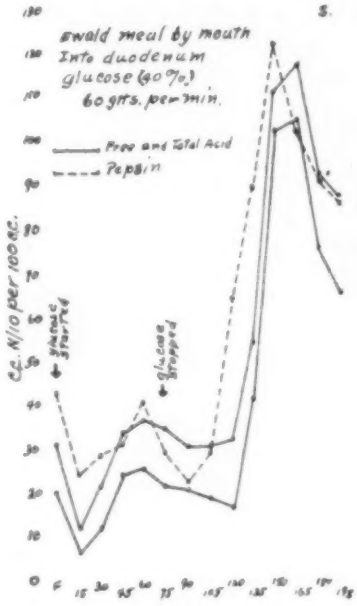

CHART 16.

Patient "S."

CHART 15. Conditions same as in chart 14 except that duodenal instillate was a 15 per cent solution of sodium oleate. The sharp rise in pepsin concentration is again seen to just precede the secondary rise in acid concentration.

CHART 16. Shows the same to be true as in chart 14, but now following the duodenal instillation of a 40 per cent glucose solution.

secretion. Such an opinion also finds support in the experiments of Orbeli [15] who found that oil in the duodenum failed to retard gastric secretion in dogs after the vagi were sectioned.

Enzyme secretion paralleled that of the acid and chlorides even to the point of showing the sharp secondary rise following the depression (charts 13, 14, 15, and 16). After the duodenal instillation was stopped, the mechanism of pepsin secretion almost invariably appeared to recover a little before the acid-and-chloride mechanism. This was shown by the earlier secondary rise in pepsin concentration when compared with the acid-and-chloride rise.

Summary

Our studies have shown consistent marked depressions of gastric secretion in man when neutral fats, fatty acids and soaps in proper concentrations were instilled into the duodenum simultaneously with the mouth meal. All secretory fractions were involved: acid, chloride, and enzymes. This depression of secretion continued for a considerable period after the instillation of the stimulant was stopped. A secondary sharp rise in gastric secretion was nearly always observed after the duodenal stimulating effect was overcome. We have not been able to confirm the opinion that this secondary rise in secretion is dependent upon the formation of soaps in the upper intestine, whose action is supposed to cause stimulation of gastric secretion. The duodenal instillation of a representative soap, such as sodium oleate, in proper concentration (15 per cent), has produced, just as oil, first depression then rise in secretion.

We have frequently seen the sharp rise of gastric secretion after the depression stage from agents other than fats. The result obtained with 40 per cent glucose, used to illustrate the action of agents other than fat or fat derivatives, represents the most striking secondary rise of secretion. Obviously, the question of soap formation is not here involved.

By the use of duodenal instillates of different concentrations (2 per cent and 15 per cent sodium oleate), we saw a difference between the thresholds of response of the gastric-motor and secretory mechanisms. The motor mechanism appears to have a lower threshold than the secretory. The mechanism of enzyme secretion also appears to be influenced differently from the acid mechanism. This is seen in the almost consistent earlier rise in enzyme concentration after the duodenal stimulant is stopped.

The question was raised whether the secondary rise in the gastric secretion, following the secretory depression from the duodenal instillation of oil, might not represent a discharge of secretion stored up during the depression period.

We believe that the duodenal influence is exerted chiefly, if not entirely, upon the psychic phase of gastric secretion; and, further, that this phase represents the important one. This is based upon the prevention of the stimulation of gastric secretion during insulin hypoglycemia, and upon the failure of duodenal stimulation to prevent a rise in gastric secretion following histamine injection.

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OBSERVATIONS ON THE SPECIFIC TREATMENT (TYPE A ANTISERUM) OF STAPHYLOCOCCAL SEPTICEMIA *

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EARLIER communications from this laboratory [1, 2, 3, 4, 5] recorded the partition of staphylococci into two specific groups, which were designated as Types A and B. The differentiation of the types was established primarily by immunological and chemical differences between the intracellular polysaccharides extracted from the respective organisms, and secondarily by the biological distinction that Type A strains are derived from pathogenic conditions, while Type B strains are apparently saprophytic. Other workers [6, 7, 8, 9] have since confirmed these observations and have, in fact, even discovered additional types among the non-pathogenic strains.[6, 9] At a later date,[10] the determination of types was simplified by the mannite fermentation test, which separates Type A from Type B by the ability of the former to metabolize acid from this sugar. The usefulness of this method, also, has received corroboration from several laboratories.[6, 9, 11]

Subsequent investigation on skin reactions [12] of normal individuals and patients to the carbohydrates of Staphylococcus indicated that while the polysaccharide of Type B is cutaneously inert, the similar preparation from Type A elicits reactions in approximately 12 per cent of normal infants and children, and 70 per cent of normal adults. An additional observation of greater importance, however, was that irrespective of skin reactivity, precipitins for the specific carbohydrate were demonstrable in the sera of only those patients suffering from severe, prolonged, generalized infection, and, indeed, only in those eventually recovering from the infection, so that latterly the appearance of precipitating antibodies in the sera of patients has been accepted as a sign of favorable prognosis.

In reflecting upon the significance of the presence of precipitins only in the sera of patients recovering from critical infection, the possible functioning of these antibodies in the mechanism of recovery, perhaps in an anti-invasive capacity, was considered. Accordingly it was proposed to treat patients with staphylococcal septicemia with antiserum containing a high titre of the precipitins capable of reacting with the specific carbohydrates. While conclusive evidence is not yet available to indicate the validity of this hypothesis, i.e., that anticarbohydrate antibodies resist invasion, the results observed with such antisera appear to be of sufficient interest to justify a communication at this time.

* Read at the New Orleans Meeting of the American College of Physicians, March 27, 1939.

From the Department of Ophthalmology, Washington University School of Medicine, Saint Louis.

Conducted under a grant from the Commonwealth Fund of New York.

Methods

Preparation of Antisera. All the antisera utilized in this study have been prepared in rabbits. No special emphasis, however, is laid on rabbit antiserum as possessing any special virtues, since the immunization of rabbits was a matter of convenience and expediency, and it is probable that antiserum from other animals may be equally effective. While still experimenting with methods of serum production, the following is the routine in use at present. Young cultures (18 to 20 hours) grown in veal infusion broth are killed by the addition of 0.2 per cent formalin. Intravenous injections are then made in series of three successive days followed by an intermission of four days. Beginning with a dosage of 0.5 c.c. of culture daily in the first series of injections, the quantity is increased 0.5 c.c. each three-day period until 2.0 c.c. are given. Ten days after the last injection of formalinized cultures, the animals are bled for 50 c.c. or more from the ear vein. The serum from this blood is subsequently processed and reserved for future therapeutic use. Five days later, immunization is resumed with the intravenous administration of living organisms. An injection 0.5 c.c. in volume is given every fifth day, starting with 0.1 c.c. of broth culture diluted to the proper amount, and the dosage is increased each time by 0.1 c.c. of culture. Ten days after the fifth injection (0.5 c.c. of culture), the animals are bled again from the ear vein. The injection of live cultures is repeated as before after five days intermission, and this procedure is conducted as long as the animals tolerate the immunization. It must be admitted that prolonged immunization renders the animals incapable of use, because they become emaciated, the antibody response is greatly reduced, and death frequently intervenes. It does not seem that an ideal method of immunization has yet been attained; several methods have been tried, and while the one described is the best thus far employed and is in use at the present time, improvements are still being sought. Frequent examination made with the sera selected for therapeutic use revealed the absence of so-called antitoxin.

Processing of Antisera. Because of the original toxicity of rabbit serum, an effort has been made at detoxification. For this purpose the method recommended by Goodner, Horsfall, and Dubos,[13] of adsorption with kaolin and subsequent heating, has been adopted. It has been found that this method requires further improvement, since it is incompletely and irregularly successful.

Administration of Antisera. Because of the widely divergent manifestations accompanying staphylococcal septicemia, it has been difficult to standardize treatment. Each case studied thus far has been a therapeutic problem in itself and has been treated differently from the others. In general, however, 1 c.c. of antiserum in 10 c.c. of saline is injected intravenously as a test dose. If within an hour no significant changes occur in blood pressure (reduction of 15 mm. or more) and respiration (15 beats or more per minute), 50 c.c. of serum diluted in saline may be given intra-

venously, the injection being made slowly, with adrenalin ready for immediate use if indicated. The treatment from then on is based on the clinical signs and the record of blood cultures. Injections may be repeated once or twice daily with 25 or 50 c.c. quantities, and the injections continued as long as the clinical indications demand additional serum. It may be desirable occasionally to continue later administration of serum by giving injections of 15 to 25 c.c. intramuscularly rather than intravenously.

Skin Test to Carbohydrate. In order to measure the adequateness of serum therapy and the development of immunity, use has been made of the skin test to the staphylococcal polysaccharides. This consists of the intracutaneous injection of 0.2 c.c. of a 1 : 100,000 dilution of Type A carbohydrate, and for purposes of control an equivalent quantity of Type B carbohydrate. The appearance of an immediate wheal and erythema reaction to the Type A carbohydrate alone is interpreted as a sign of immunity, and serum therapy may be discontinued. Whether, however, this test is actually as valuable as it seems to be at the present time requires a much larger number of observations before rendering a final decision. In this study, none of the patients tested [15] reacted when first observed, but, of those recovering, all tested became reactive.

Clinical Observations

Up to the time of writing, 17 patients have been treated with antistaphylococcus Type A serum. In each instance the presence of staphylococcal septicemia was established by repeated blood cultures (i.e., at least two) before administration of serum. It is of interest to add at this point that all of the cultures from blood, as well as those isolated from the primary and, in some cases, the secondary foci, were found to ferment mannite and to contain Type A carbohydrate. As was to be expected, the septicemia was always secondary to a primary lesion.

For purposes of more facile presentation, it is desirable to describe the results obtained as observations on patients who survived and those who died.

Synopsis of Patients with Recovery. Of the 17 patients treated with antistaphylococcus Type A serum, seven survived. Of these, three were children with a diagnosis of osteomyelitis as well as bacteremia; two were adults who started with furunculosis and progressed to bacteremia, one even exhibiting clinical signs, verified by the laboratory, of renal abscess; another adult began with an infected blister which advanced into a thrombophlebitis, pyonephritis, cystitis, severe decubitus eventually requiring plastic surgery, and bronchopneumonia; and finally, another adult who, with a primary abscess of the right face, developed bacteremia and bronchopneumonia overnight, the latter condition also due to Staphylococcus. These patients received total amounts of serum varying from 75 c.c. to 160 c.c. over periods ranging from five to seven days. In addition to the serum, surgical care

was given wherever indicated, and blood transfusions supplied when necessary.

In making an analysis of these cases, it is obviously difficult to state whether the patients would have survived in the absence of serum therapy, or whether the antiserum was the decisive factor in recovery. Upon retrospection, it is not unlikely that while the antiserum was undoubtedly an adjuvant measure in the three children with osteomyelitis, recovery would probably have occurred despite their severe and critical infection. In the remaining four patients, the infection was particularly acute and critical, so that the physician in charge in each case had begun to concede the case as hopeless. It may well be, therefore, that in these instances Type A antiserum was more than merely adjuvant. It must be admitted, however, that in the ultimate analysis, the evidence on whether survival was the result of the antiserum is inconclusive, just as necessarily must be the case with all contrary-to-fact conditions. If, however, the following observations have any significance: that, in general, bacteremia, measured by colonies per c.c. of blood, was reduced with the first large dose of serum; that the blood usually became sterile within two to four days following commencement of serum therapy; that in those instances when the blood was not immediately sterile, growth of the cultures was retarded to three, four, and five days' incubation, which is in contrast to the usual overnight growth of the cultures before administration of serum, then it would seem that even if a certain degree of doubt regarding the indispensability of the antiserum is entertained, there was with its use definite action on the bacteremia of the patients reviewed above.

The therapeutic effect of the antistaphylococcus serum appears not to be the dramatic, rapid detoxification and defervescence observed with antipneumococcus serum. Recovery is more gradual and the course of the infection still remains prolonged and erratic: thus, in two patients there was a transient bacteremia of one day's duration following periods of sterile blood cultures. The possible reasons for this gradual recovery will be discussed later.

However, no alarming effects were observed in any of the patients during or following the injection of antiserum. In one patient, however, since the preceding injection caused a certain degree of respiratory embarrassment as well as a rash, possible difficulty was avoided by administering the serum mixed with adrenalin. In four of the seven patients surviving the infection, serum sickness was observed. In each individual, this complication appeared in a mild form, consisting of edema and urticaria, and it lasted from one to two days.

Synopsis of Patients with Fatal Infection. The foregoing observations indicate that antistaphylococcus serum, Type A, may confer on the patient a certain measure of benefit by reducing the duration of septicemia and occasionally may even be a deciding factor in survival. With recovery resulting, however, the evidence concerning either its degree of effectiveness or

manner of operation must necessarily be incomplete. Because of the advantage of postmortem observation, on the other hand, it becomes possible to observe in the fatal cases what the influence of the antiserum has been, and how it has affected the infection. In other words, the opportunity is presented to obtain information otherwise available only through direct animal experimentation. Ultimately, all that can be said about surviving patients is that they have survived, while in dying patients what has actually happened may be studied. Fortunately, autopsies were conducted on all the fatal cases, and it is particularly interesting to review the clinical and pathological records of these patients.

As said above, 10 of the 17 patients treated with Type A antiserum eventually succumbed. Four of the patients died within six to 20 hours after serum therapy was begun: of these, two were infants whose original difficulties were feeding problems and in whom the infection appeared to be terminal; the other two, one adult and one infant, were genuine staphylococcal infections. In any case, it is obvious that administration of serum was begun too late in the course of the infection, and indeed they furnish little if any evidence of the potency or impotency of the serum.

In four patients, the blood was sterilized even though death ensued. In one, a boy of 14 years with multiple abscesses, osteomyelitis, and bacteremia, the blood became free of staphylococci after injection of 43 c.c. of antiserum, which was the total supply on hand at the time. After three days during which the blood was found to be free of staphylococci, bacteremia reappeared, and in the absence of further serum treatment the patient progressed rapidly from bad to worse, and at necropsy exhibited all the typical signs of staphylococcal infection (i.e., multiple abscesses of the liver, spleen, kidneys, lungs, heart muscle, and pericardium).

In the remaining three whose blood became sterile following administration of Type A serum, one was a girl of 11 years, who, originally suffering from peritonitis and bacteremia due to Type I pneumococcus, had received prolonged treatment with sulfanilamide which was followed by agranulocytic leukopenia (i.e., for one week the total number of white cells was close to 200, with not a single polymorphonuclear cell to be seen in repeated smears). This condition was quickly followed by Ludwig's angina and staphylococcal septicemia, and her chances of survival under the circumstances appeared extremely poor. A total of 350 c.c. of serum was administered, her blood culture became sterile, and her white blood cell count reached 22,000, with close to 80 per cent of the cells neutrophiles. An operation performed on the throat to drain the parotid led to severe and repeated hemorrhages which were not controlled by transfusions and other measures, and the child died within 48 hours. Postmortem examination revealed the astonishing picture of not a single gross abscess in any of the organs or tissue. A blood culture made at the time yielded only hemolytic streptococci, which were considered as terminal invaders of no particular importance. Later, in studying sections, a small, well-organized abscess was located in the lung, much too small

to be within macroscopic visibility. When it is realized that the child ran a course of severe staphylococcal septicemia lasting almost three weeks, it must be admitted that the absence of metastatic abscesses is an extremely unusual picture in this kind of infection.

The second patient entered the hospital with a severe arsphenamine dermatitis with accompanying impaired function of liver and kidney. Perhaps due to the condition of the skin, furunculosis developed and then a bacteremia. The blood became sterile and the patient appeared to be progressing favorably, with specific precipitins demonstrable in the blood, when he died suddenly. Again, postmortem examination revealed no abscess formation in any of the organs, and death was ascribed by the pathologist to arsenic poisoning, since a culture of the heart blood yielded no organisms and the tissue changes justified such a diagnosis.

The last patient of this group, an adult, 58 years old, entered the hospital with a swollen, red, painful wrist and knee, acutely ill and toxic. Blood cultures taken at this time yielded staphylococci. In a few days there was suppuration of the scrotum from which staphylococci were recovered. Within two days 90 c.c. of serum were administered, which appeared to be sufficient to sterilize the blood. Two days later, the patient gave signs of lobar pneumonia, and he died on the following day. At autopsy, absence of abscesses was again noted. The lungs showed typical lobar pneumonia. Cultures taken of the heart blood were sterile, while from the lungs pneumococcus, Type VIII, was isolated.

The remaining two of the patients who died showed typical signs of staphylococcal infection at necropsy. One, a small boy, 1½ years old, had obviously progressed to a point beyond help. There had been suppuration and erosion through the heart wall causing a hemorrhage into the pericardial sac. The hemorrhage was of sufficient duration, moreover, to have become organized and was adherent to both the pericardial and heart wall, and in the resulting blood clot were grossly visible many colonies of staphylococci. Osteomyelitis of the right tibia had become so advanced that the bone was literally floating in pus. It was the opinion of the pathologist that the appearance of the blood clot suggested its antecedence over the administration of serum.

The last patient, an adult of 60 years, from an infected pimple on the nose, progressed to a bronchopneumonia, septicemia, and nephritis. After three weeks' treatment, first with sulfanilamide, then with 100,000 units of antitoxin a day for 10 days, and transfusions every other day, he showed no improvement. He was given 200 c.c. of Type A antiserum without avail. While the septicemia had been reduced during the treatment, it was not suppressed completely. At autopsy, the multiple abscesses in the various organs (liver, kidney, lung, and heart) were typical of the infection.

Thus, then, it is seen that of the 10 patients who died, four were so far advanced as to last less than one day; four had had their blood sterilized, one becoming septicemic again after discontinuance of serum as described

above, while the other three died without the characteristic picture of staphylococcal infection, one of exsanguination, one of arsenic poisoning, and one of pneumonia due to pneumococcus Type VIII. The remaining two died of typical staphylococcal infection, but it is quite likely that serum therapy was begun too late in the progress of the disease. In any case, these are the only cases that can logically be considered as possible failures of the antiserum.

Discussion

Preliminary to an appraisal of the data assembled in this report, it is desirable to point out the cardinal characteristics of severe staphylococcal infection. It is common knowledge that while the large majority of staphylococcal manifestations are usually of minor significance, the possibility is always present of the infection extending into a spreading lymphangitis which may reach the regional lymph glands and may eventually even burst through the tissue barriers into the blood stream. As a localized abscess, however, the condition usually terminates with healing, despite its tendency to persistent recurrences, ultimately its importance being a passing one. Septicemia, on the contrary, is a serious and severe complication; secondary to a local lesion, it incites in the various tissues and organs metastatic abscesses which in turn discharge into the blood stream, thus creating a vicious cycle soon beyond medical and surgical control. Consequently, if any treatment based on specific antiserum is to be effective, it must eliminate or reduce considerably the conditions which promote septicemia; it must check septicemia when present; and it must prevent the formation of metastatic foci. Furthermore, it is necessary to supplement serum therapy with surgical drainage, thus allowing the abscesses to discharge outward rather than into the blood stream. Moreover, if septicemia has been prolonged before antiserum is administered, it is obvious that multiple abscesses may have already been formed in various parts of the body, with the result that, depending upon the extensiveness of the dissemination, both the resistance of the individual and the protective capacity of the serum are completely overwhelmed and death ensues. (Cf. last two patients of second synopsis.)

In contrast to the invasive element of staphylococcal infection briefly reviewed in the preceding paragraph, consideration must be given to the toxic factors as well. During the infection there is a great amount of tissue destruction causing the liberation of toxic substances, which are absorbed to a greater or less extent. In addition, there are metabolic products of growth elaborated by the staphylococcus which are also toxic and also absorbed by the tissues. It is a difficult matter for any variety of antiserum to neutralize all these substances, as is borne out by the use of current antitoxic sera.[14] It is similarly difficult to prevent entirely absorption of the toxic materials by surgical drainage. Consequently, even when septicemia is suppressed completely, the patient inevitably remains toxic and continues in this condition until the various foci have healed. It is small wonder, then,

that even in surviving patients, the course of recovery is apt to be turbulent and prolonged.

It would seem, therefore, that in any form of treatment the most important factor is the prevention or elimination of septicemia. Localized infections are managed successfully by the patient, and the toxicity of the discharging material (bacterial and tissue) is too diversified to allow complete specific neutralization. It was consequently proposed in beginning this study to learn if possible the conditions operating in opposition to the invasiveness of Staphylococcus.

The facts outlined in the present report are that rabbit antiserum was prepared to contain antibodies that react with the carbohydrate characteristic of Staphylococcus, Type A; this antiserum was used in the treatment of 17 patients with staphylococcal septicemia secondary to a primary lesion; seven patients survived, while 10 died; of those dying, four were started on treatment too late in the disease; one died after checking the septicemia, but treatment was insufficient because the supply of serum became exhausted; three died of other causes after sterilization of the blood, as verified by postmortem examination; and two, whose treatment was delayed, possibly beyond help, died of typical staphylococcal infection; of the 17 patients, therefore, septicemia was eradicated successfully in 11. If, however, allowance is made for the patients who died in less than 24 hours after inception of serum treatment, the analysis indicates the antiserum was successful in 11 of 13 trials.

It seems, therefore, that under certain conditions, the experimental Type A antiserum employed in this study may be of value in checking septicemia and even in preventing the formation of metastatic abscesses. The antiserum was unable to eliminate the toxemia observed in all the patients, and whether reinforcement with antitoxin will broaden its usefulness is a problem for future study. In any case, it seems wise to supplement the antiserum with supportive measures, particularly surgical drainage and blood transfusions. It is realized that the total number of patients treated thus far form too small a group to allow any conclusions. All that can be said at the present time is that the results observed with this antiserum are encouraging and perhaps hopeful.

Summary and Conclusions

1. Seventeen patients suffering with staphylococcal septicemia secondary to a primary lesion yielded on culture staphylococci belonging to Type A and capable of fermenting mannite.

2. All the patients were treated with Type A antiserum prepared in rabbits and were given in addition whatever supplementary measures were indicated (e.g., surgical drainage, blood transfusions, etc.).

3. The untoward reactions ascribable to the serum were mild, and in four patients the treatment was followed by serum sickness.

4. The skin reaction to the carbohydrate of Type A is suggested as an index of sufficient treatment.

5. Of the 17 patients treated with Type A antiserum, seven recovered and 10 died.

6. Of the 10 patients dying, four died before the end of the first day of treatment, four had developed sterile blood cultures (and of these, three died of other causes) and two died with typical signs of staphylococcal infection.

7. Exclusive of the four patients who succumbed within the first day, then, Type A antiserum apparently sterilized the blood in 11 of 13 patients.

The writer acknowledges with appreciation and gratitude the assistance of the following physicians for both referring the patients and assuming their complete care and responsibility:

Dr. Alexis F. Hartmann, Children's Hospital, St. Louis.....seven patients
Dr. David P. Barr, Barnes Hospital, St. Louis .....three patients
Dr. Thomas P. Findley, Jr., City Hospital, St. Louis .....one patient
Dr. Joseph C. Jaudon, Children's Hospital, St. Louis .....one patient
Dr. Park J. White, Children's Hospital, St. Louis .....one patient
Dr. Joseph C. Edwards, City Hospital, St. Louis .....one patient
Dr. Walter J. Siebert, DePaul Hospital, St. Louis .....one patient
Dr. J. G. Probstein, Jewish Hospital, St. Louis .....one patient
Dr. Paul F. Stookey, St. Mary's Hospital, Kansas City, Mo. .....one patient

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BENIGN AND MALIGNANT GASTRIC ULCERS: THEIR RELATION AND CLINICAL DIFFERENTIATION *

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THE purpose of this paper is to consider briefly the relationship between benign and malignant gastric ulcers, the clinical differentiation of the two lesions, and the therapeutic implications.

RELATIONSHIP

A few years after Cruveilhier differentiated gastric ulcer from gastric carcinoma, Rokitansky described a case interpreted as showing the carcinomatous transformation of a benign ulcer. An enormous controversial literature has since developed regarding, first, the existence of carcinomatous degeneration in ulcer, and, secondly, the incidence of such a process. A critical review of the subject has led me to doubt the existence of such a transformation. The alleged evidence for such a change is based on pathologic and clinical findings. To support this viewpoint pathologically, carcinoma must be found and proof of the original benign nature of the lesion established. The difficulty in a given case does not consist usually in establishing the presence of the standard criteria of malignancy, but in proving the initial benign nature of the lesion. It is customary to demand that the floor of the ulcer be composed of dense, fibrous and granulation tissue not infiltrated with tumor cells and that there be complete destruction of an area of muscle corresponding in size roughly to the ulcer. Fusion or close approximation of the muscularis mucosae and muscularis at the edge of the ulcer and endarteritis obliterans are other signs suggestive of preëxistent benign ulcer. It is recognized, however, that none of these is pathognomonic of a preëxistent benign ulcer and that any and all of them may be found with primary carcinoma. Histologically, therefore, the evidence of an initial benign ulcer in a carcinomatous lesion is never conclusive.[1]

The clinical proof usually adduced is also not conclusive. The presence of epigastric distress for many years, even if it is of the typical ulcer type, may have no relation to the carcinoma, for numerous cases of neoplasm have been described as arising in stomachs containing gastric or duodenal ulcer but entirely independent of these lesions. Even the case described by Scott and Mider [2] of carcinoma occurring at the site of an acutely perforated gastric ulcer surgically repaired two years previously may be looked upon, and I think should be looked upon, as a slowly growing primary carcinoma which had undergone peptic ulceration. The presence of free acid in the gastric

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content has been looked upon as "the crucial factor" in the diagnosis of preëxistent benign ulcer.[3] On the contrary, however, the evidence offered in support of this concept may equally well be interpreted to support the opposite view, namely, that acid gastric juice may destroy the carcinoma so completely and attack the normal tissue to such an extent as to mimic benign ulcer completely.[4]

The following case is described in considerable detail as illustration of this point. It shows the extent to which an apparently primary gastric carcinoma may undergo peptic ulceration with healing, scar-tissue formation, and even epithelization, and thus simulate a benign ulcer.

The patient, a male 50 years of age, entered the Clinics November 19, 1938, on the service of Dr. A. Hughes Bryan complaining of sharp, knifelike pain in the middle of the sternum of 12 hours' duration. Occasional attacks of vomiting had occurred during the preceding year, approximately one every three to four weeks, coming on one to one and a half hours after meals. Five months prior to admission the patient became conscious of a heavy, dragging sensation in the epigastrium. A roentgen-ray examination was said to have disclosed the presence of a gastric ulcer for which a regimen of milk and cream and powders was prescribed. A subsequent roentgen-ray examination was said to have disclosed no ulcer. The patient continued the milk and cream and powder program, felt improved, but lost 20 pounds in three months. There was no history of indigestion or epigastric distress prior to June 1938.

Physical examination disclosed no significant abnormality. The red blood count on admission was 3.95 million; hemoglobin, 72 per cent (Dare); white blood count, 10,000. The histamine test of gastric secretion December 23, 1938, revealed a maximum free acidity of 106 with a maximum 10-minute volume of 24 c.c. The stool examinations for occult blood varied from negative to strongly positive. Roentgen-ray examination on November 21, 1938, had disclosed a frank early stage lesion of the seventh thoracic vertebra, presumably a metastatic neoplasm, and a lesion in the body of the sternum interpreted either as gumma or neoplasm. The gastric film contained a small, pointed projection at the lesser curvature of the stomach just proximal to the pyloric antrum, interpreted as being possibly a very small lesser curvature neoplasm with a tiny crater (figure 1). At a subsequent examination December 2, 1938, this small niche was not found. Two months later, February 3, 1939, the niche was again found roentgenologically and, in view of the gastroscopic findings, interpreted as an infiltrating, ulcerating type of carcinoma. Lesions noted in the right ischium, ilium, and femoral neck were interpreted as metastatic.

Gastroscopic examinations by Dr. Rudolf Schindler were reported as follows:

December 15, 1938. Definite pathology is found at the angulus. It is not a parabolic curve. Its anterior branch presents a protruding node. On the top of its arch, a large, rather round, dark red, mucosal hemorrhage is seen below which the arch is flattened and stiff. There are nodes protruding from the posterior wall of the antrum. The stiffness of the infiltrated portions is marked. No craterlike excavation or ulceration is observed. The mucosa is pale throughout but not atrophic. At several places pigment spots and stripes are observed.

Impression: Diffusely infiltrative lesion of the angulus. (I do not believe this is a simple gastritis; probably it is a type IV infiltrative carcinoma, although other infiltrative lesions cannot be excluded with certainty.)

December 22, 1938. The interpretation of this gastroscopic picture is exceedingly difficult. The lesions today are entirely different from those seen at the last examination. The angulus and the contracting pylorus are well observed. The angulus is not entirely round, but it is less stiff than it was when seen before. The dark red

hemorrhage has disappeared. Instead of it, a very small, round, yellowish, superficial ulceration is seen with many superficial mucosal hemorrhages in the vicinity. The entire mucosa is paler than at the last examination. I should estimate the hemoglobin content, from the aspect of this mucosa, to be not higher than 50 per cent.

FIG. 1. Small, penetrating, carcinomatous ulcer of the lesser curvature.

Impression: There is definite pathology of the stomach present, but I am unable to make a definite diagnosis. The reduction of the infiltration speaks against malignancy. The small ulcer at the angulus probably is a gastritic erosion. Most conspicuous are the pallor and the many mucosal hemorrhages. I remember a similar case in which a diffused hemorrhagic condition covered a diffusely infiltrated carcinoma.

December 31, 1938. Again the picture has changed. The entire gastric mucosa looks extremely pale and I should think the hemoglobin cannot be over 20 per cent. . . .

At the highest point of the angulus, exactly in the lesser curvature, the interesting phenomenon of an acute mucosal bleeding is observed. A dark red bead of clotted blood is seen hanging into the lumen and lighter red blood falls down in drops from the tip of this clot into the stomach. This continuous bleeding makes this examination difficult; nevertheless, I have the impression that the anterior margin of the angulus is slightly infiltrated. . . .

Impression: (1) Acute, diffusely bleeding lesion of the angulus. I am unable to determine the exact nature of this lesion. (2) Extreme pallor of the gastric mucosa.

February 1, 1939. The examination is a complete one. The entire antrum is seen, even its lesser curvature. The pylorus contracts regularly and energetically. I have the indefinite impression that the upper portions of the anterior wall of the antrum are slightly stiff and protruded. In the lesser curvature above the angulus, again definite pathology is found. There is an infiltrated area approximately 4.5 to 5 cm. in diameter which showed many nodes and nodules. No sharp limit to this infiltration is seen. In its center a yellowish ulceration is observed, the margin of which is not sharp at all but blending throughout with the surrounding mucosa. The upper edge of the infiltrated area is seen 9.5 cm. below the cardia. No mucosal changes, especially no atrophy, are observed.

Impression: I cannot hesitate any longer to make the definite diagnosis of an ulcerative carcinoma, type IV, in the lesser curvature above the angulus.

The pain over the sternum continued, pain in the right hip and leg appeared, loss of weight and strength progressed. Pallor developed and increased. The red blood count dropped to 2.36 million with a hemoglobin of 49 per cent on December 31, 1938, to 1.93 million with a hemoglobin of 38 per cent on January 4, 1939, and, in spite of seven blood transfusions of approximately 600 c.c. each, reached a low of 800,000 on the day of death, February 5, 1939. The terminal picture was that of thrombocytopenic purpura and anemia secondary to extensive carcinomatosis.

At autopsy (Dr. Paul Steiner, Department of Pathology), the essential final anatomic diagnoses were:

1. Small, ulcerated, prepyloric adenocarcinoma of the stomach.
2. Independent carcinoma, or implantation metastasis in the mucosa of the gastric fundus.
3. Massive carcinoma metastases to the skeleton. Minute carcinoma metastases to lymph nodes, spleen, and lung.
4. Atrophic gastritis.
5. Marked anemia.
6. Fatty degeneration of the myocardium, liver, and kidneys.
7. Extramedullary hematopoiesis in the spleen and liver.

The gastric lesion appeared grossly as a benign ulcer 1 cm. in diameter and 1 to 3 mm. deep, located on the lesser curvature 4 cm. from the pyloric ring. Its margins were slightly reddened and slightly rolled although soft and pliable. The ulcer floor was clean except for mucus. External to this point, the serosa of the stomach showed a little puckering but no thickening. The gastric mucosa near the ulcer showed a number of soft, slightly elevated, edematous swellings. Grossly the gastric ulcer and the adjoining linear scar had the appearance of peptic ulcer and not of ulcerated gastric carcinoma. Figure 2 is a section through the carcinomatous ulcer. The floor is composed of dense, fibrous tissue replacing all layers of the gastric wall. At the margins of the ulcer are scattered, imperfectly formed tumor glands and some diffuse growth of undifferentiated carcinoma cells. Figure 3 is a higher magnification of section 1 through the margin of the lesion showing normal mucosa on the right and carcinomatous infiltration on the left. Figure 4 from section 2 shows ulceration

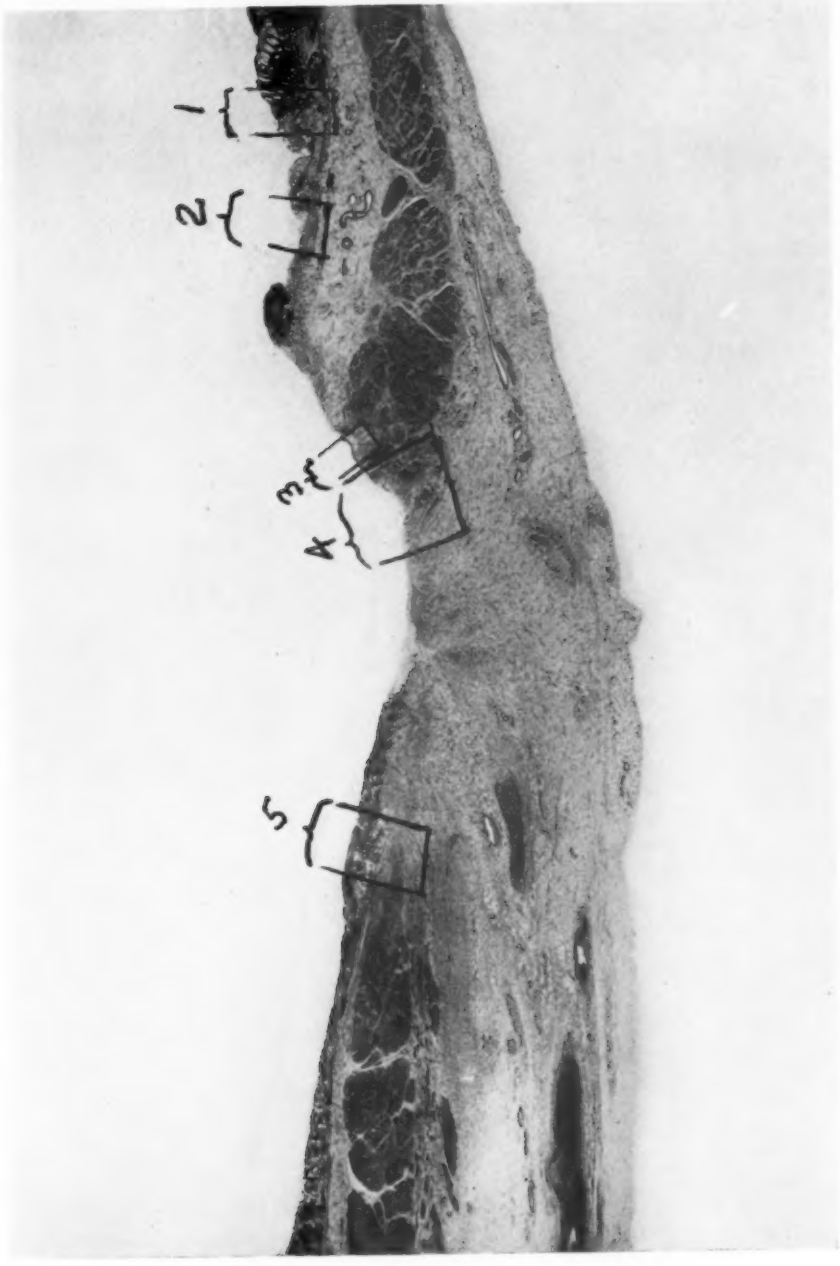

FIG. 2. Cross section through ulcerating carcinoma showing scar-tissue floor and general architecture of benign ulcer; × 6.

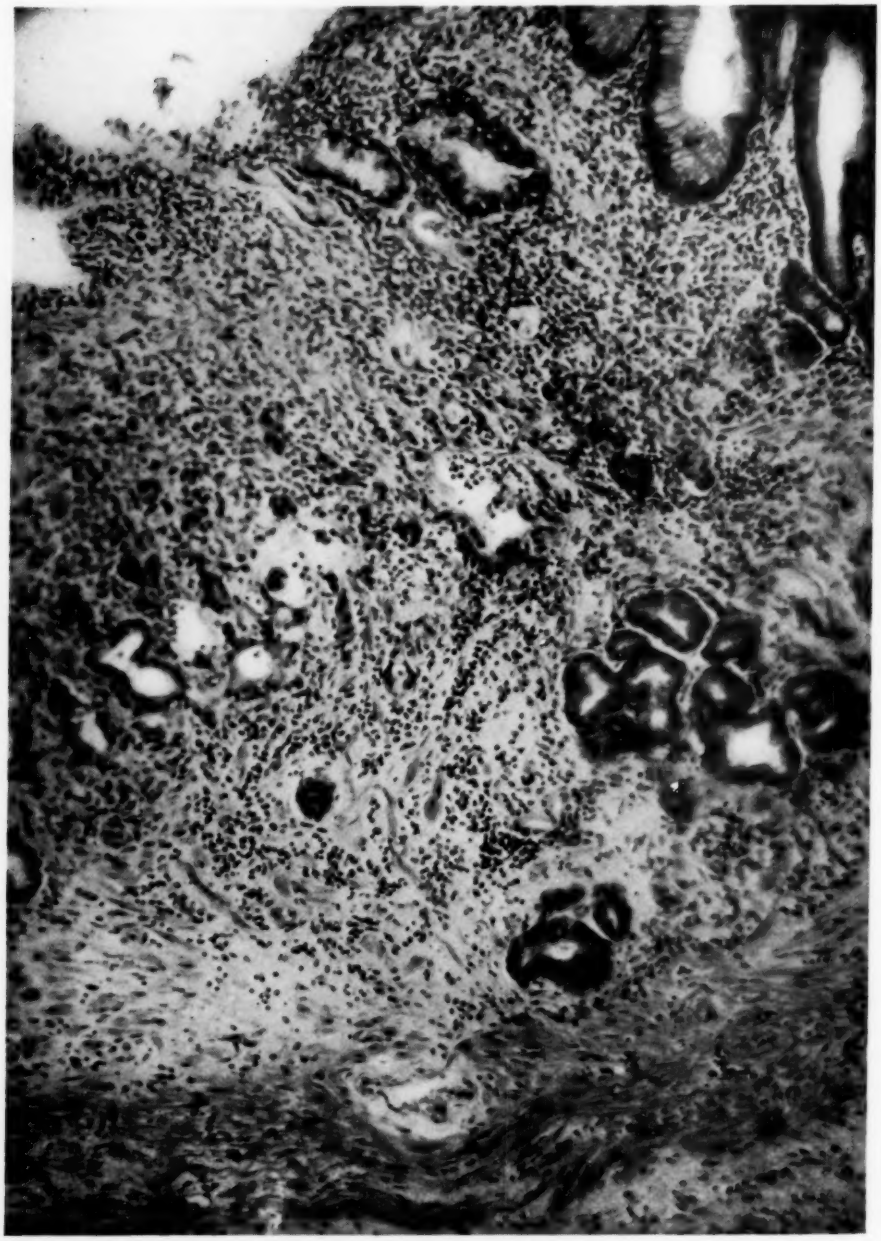

FIG. 3. Section through margin of ulcerating carcinoma showing edge of normal mucosa at right and carcinomatous infiltration at left; × 130.

FIG. 4. Ulceration in carcinoma at edge of ulcer; × 130.

in carcinoma, the muscularis mucosae being as yet intact. In figure 5 from section 3 the superficial layer of tumor cells is well shown. In figure 6 of section 4 this layer is seen growing down over, or only partially digested away from, the dense scar-tissue base. Figure 7 from section 5 in the left edge of the lesions shows diffuse adenocarcinomatous infiltration of the superficial layers of the mucosa and overlying noncancerous mucosa. The extensive carcinomatous infiltration is that of a primary gastric carcinoma, a conclusion quite in accord with the brief history, the extensive carcinomatosis, and the rapid clinical course. The structure of the ulcer must be ascribed to peptic ulceration of a primary carcinoma, producing thereby a lesion grossly indistinguishable from benign ulcer.

Extending laterally from the ulcer in the mucosa was a linear, slightly depressed and puckered scar up to 1 cm. wide and 4 cm. long, apparently lined with mucosa. Figure 8 is a cross section through this scar showing its complete reëpithelization. The carcinomatous infiltration of the epithelium with neoplastic glands beneath the muscularis mucosae is evident in figure 9.

In the fundus of the stomach about five inches from the ulcerated cancer, at a point where no lesion was grossly visible, an incidental microscopic section revealed a small superficial carcinoma located in the mucosa (figures 10 and 11). It was impossible to determine whether this was an implantation metastasis or a beginning independent cancer.

Elsewhere all portions of the stomach showed microscopic evidence of an atrophic gastritis of a moderate degree (figure 12). The mucosa was thin with a decrease in size of all parts of the glands, some cystic dilation of the glands, an increase in interglandular cells and interstitial stroma, large aggregates of lymphoid cells, and fibrous thickening of the submucosa. The changes of atrophy and metaplasia predominated over those of inflammation.

The skeleton was the site of a remarkable, diffuse, metastatic, adenocarcinomatosis involving all bones examined except a tarsal bone. Thus, dorsal and lumbar vertebral bodies, sternum, clavicle, ribs, and ischium showed replacement of the red marrow by tumor. The sternum was enlarged because of new bone produced on the surface of the old cortex by periosteal stimulation of tumor, but "while the density of the bones was about normal, the structure was not" (figure 13).

The case evidently falls in the group of diffusely infiltrative carcinomas thoroughly reviewed recently by Jarcho.[5] Evidence of initial malignancy is to be found in the brief clinical course (eight months), the early appearance of widespread metastases, the small ulcer with tumor cells infiltrating both edges and covering a portion of the base with scattered foci in the base, the carcinoma in the mucosa lining the epithelized superficial scar adjacent to the ulcer, and the gastritic changes in the mucosa elsewhere. The small carcinoma accidentally found in a fold high in the stomach could perhaps be explained as an implantation metastasis, but a more probable explanation is that of primary multicentric carcinoma developing in a mucosa undergoing neoplasia. The presence and distribution of the malignant cells in the epithelium covering the scar, figures 8 and 9, may be interpreted as being in accord with this concept. The structure of the ulcer simulating, as it does, a benign lesion with healing (even the complete healing of one defect!) may be attributed to peptic digestion (histamine free acidity, 106!). The identical gross appearance of benign and malignant ulcer is not surprising when one bears in mind that the pathogenesis of the two lesions may be in part the same, namely, "acid attack" or "peptic digestion."[6] Car-

FIG. 5. Edge of base of ulcerating carcinoma showing superficial layer of tumor cells; × 160.

FIG. 6. Scar-tissue base of ulcer with layer of cancer cells on surface of upper right edge; × 60.

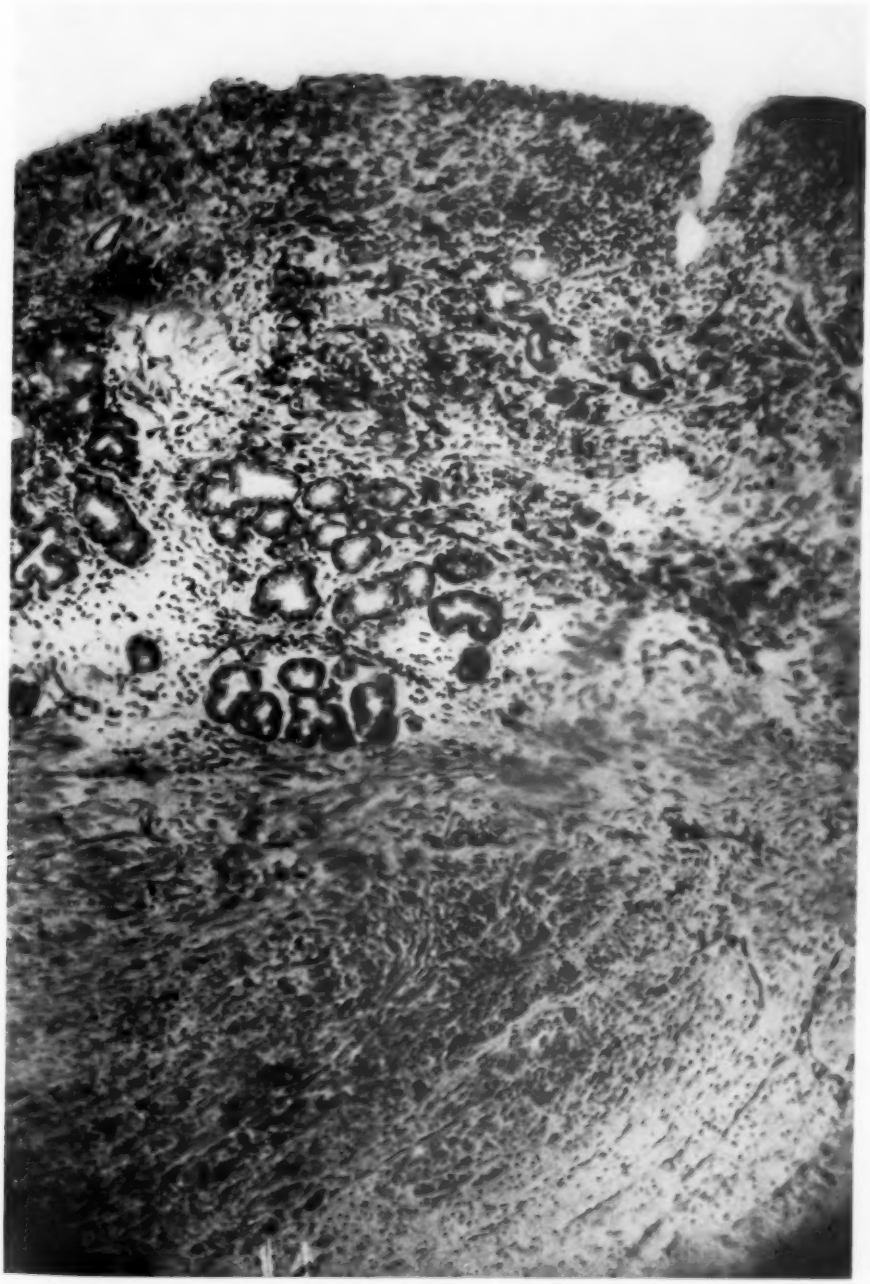

FIG. 7. Left edge of ulcerating carcinoma. Diffuse infiltration of adenocarcinoma overlying noncancerous mucosa; × 115.

FIG. 8. Section of scar adjacent to ulcer showing epithelization with mucosa containing nests of tumor cells; ×5.

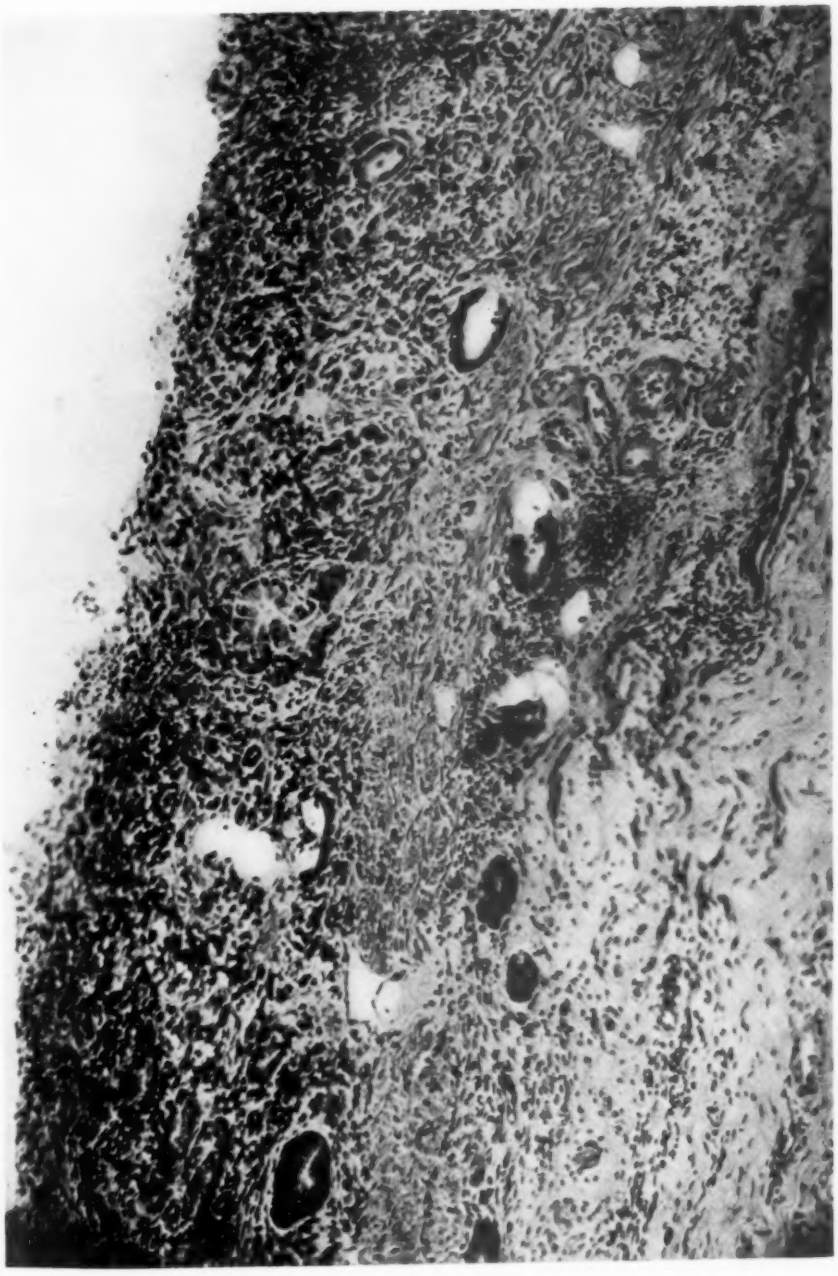

FIG. 9. Same section as in figure 8, showing carcinomatous infiltration of the epithelial layer with neoplastic glands beneath the muscularis mucosae; × 120.

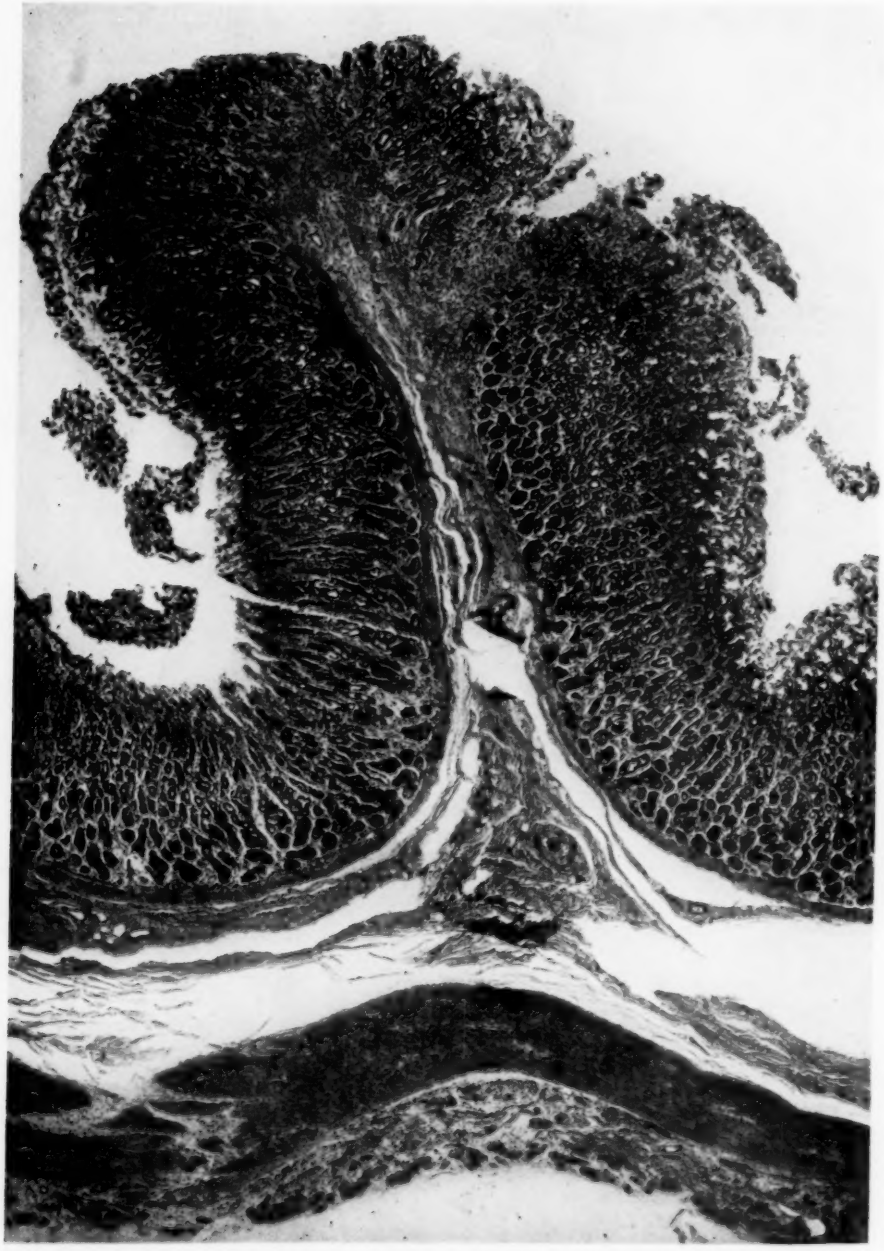

FIG. 10. Section of fold in fundus showing early carcinoma; × 30.

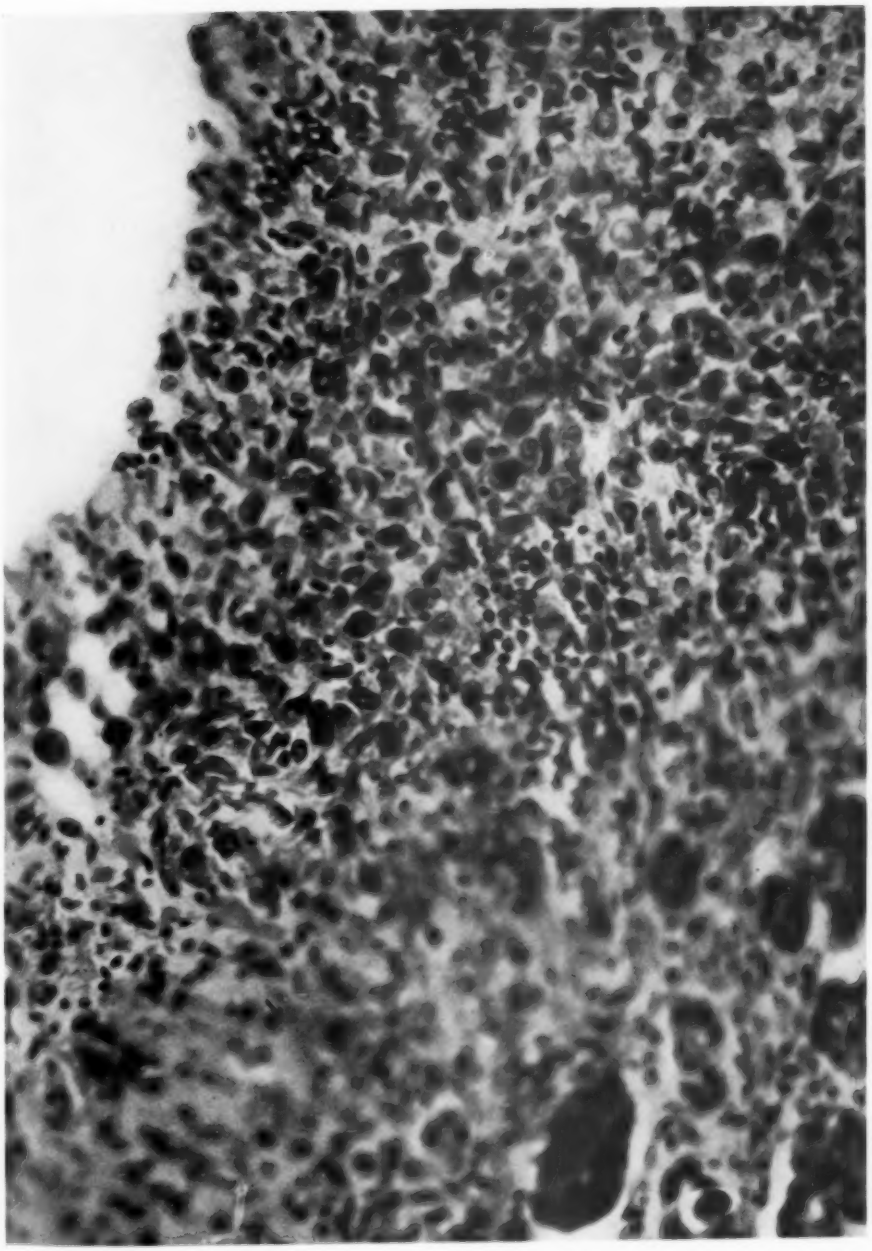

FIG. 11. Section of tumor in figure 9 showing numerous abnormal cells and abnormal, mitotic figures; ×300.

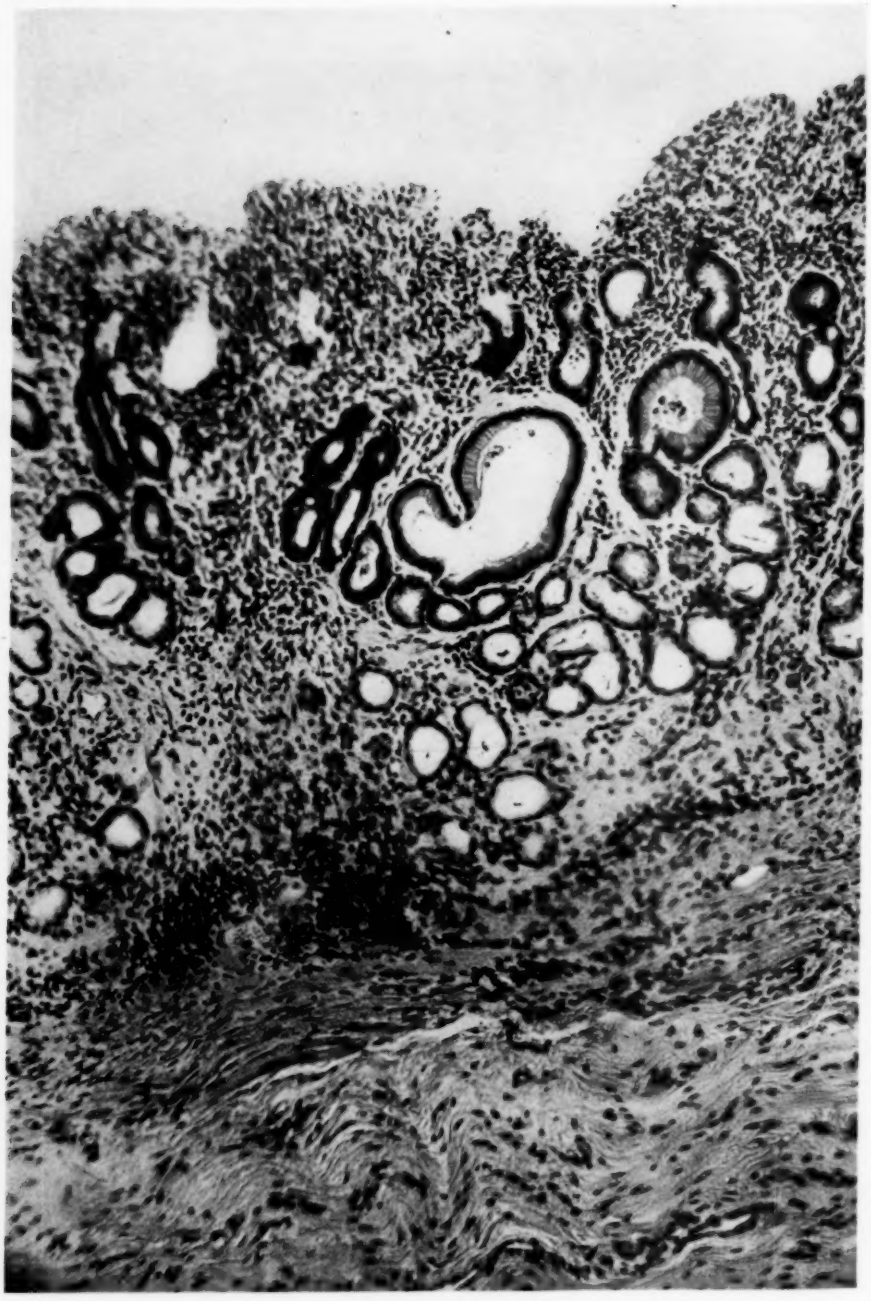

FIG. 12. Atrophic gastritis with fibrous tissue thickening of submucosa in the pyloric region not far from the ulcer; × 130.

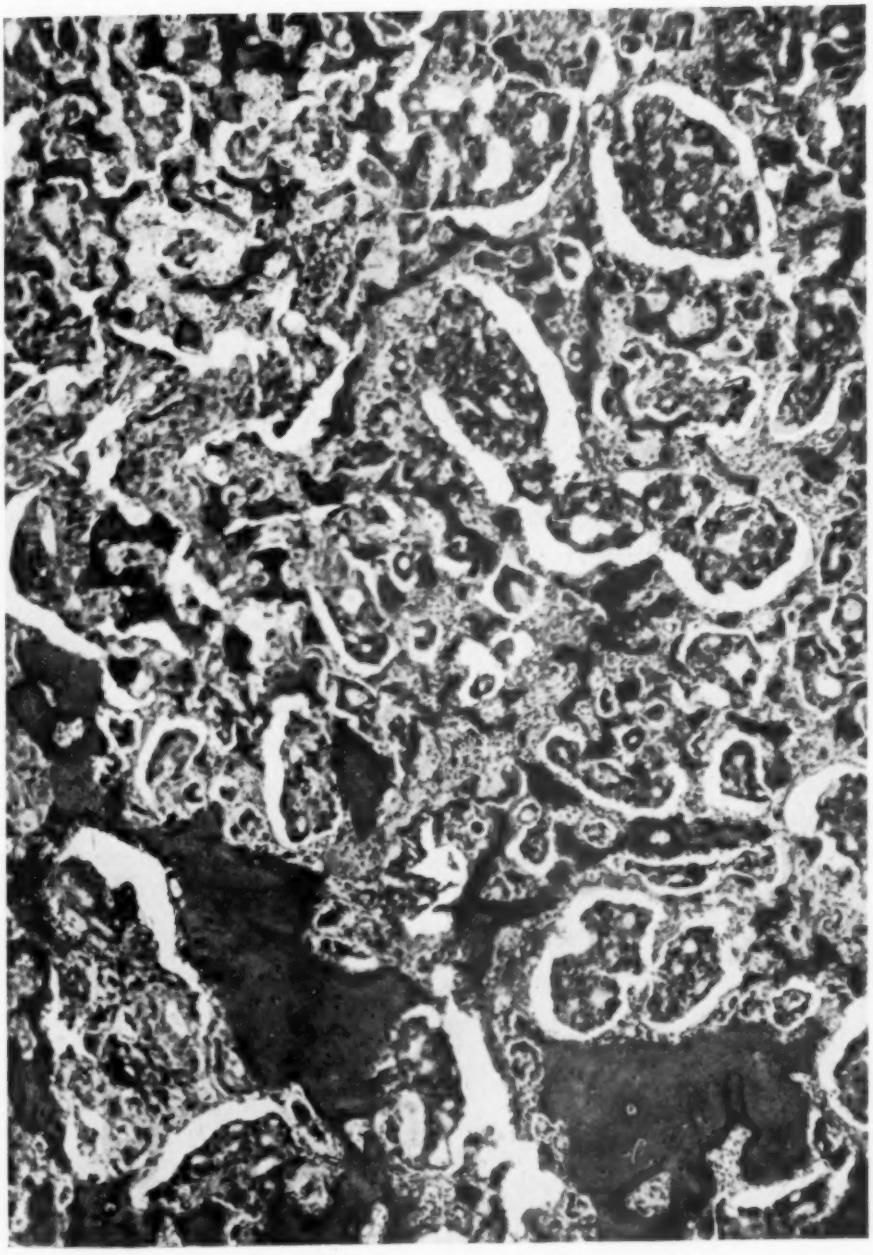

FIG. 13. Metastatic adenocarcinoma infiltrating the bone marrow (sternum); ×75.

cinomatous mucosa is probably less resistant than normal tissue to the digestive action of acid gastric juice.

Differentiation

If the concept of acid digestion of carcinomatous gastric tissue be accepted, and particularly if the concept of acid digestion of normal gastric tissue in both benign and malignant ulcer be accepted, the theoretical possibility of the complete inseparability of the two lesions must be conceded. In practice, the differentiation can, as a rule, be made, but the criteria must be critically examined. It is important to recognize at once that, while there is no pathognomonic sign to prove the benign nature of an ulcer, the total evidence available may be sufficient to make this diagnosis highly probable and, in the course of time, certain. Opinions differ as to whether in general, or indeed in a particular case, the evidence is sufficient to justify medical management and delay. Bloomfield [7] has pointed out that if the incidence of error in the clinical differentiation is not greater than the mortality rate from subtotal gastrectomy, the delay necessary is justifiable. It is difficult to be positive on this point, for the accuracy of the clinical differentiation varies from person to person just as the mortality rate from resection varies from individual to individual. Both depend upon the skill of the physician or surgeon and upon the special conditions present in the case under consideration.

The important differential points and the difficulties involved are the following:

1. Age. This is not of great diagnostic value, for carcinoma occurs in the third decade and benign gastric ulcer is common in the later decades of life.

2. Duration. A long history is said to favor benign ulcer and a short one malignancy, but carcinoma may develop in a patient with chronic distress of other origin and, conversely, benign ulcer frequently gives a history of only a few months' duration.

3. Periodicity. If the *same* distress has recurred at intervals for several years, the probability of a benign lesion is greatly enhanced, but malignant lesions, if very slow growing, may display asymptomatic periods. Benign ulcer, on the other hand, may give no history of periodicity.

4. Relationship of the distress to meal taking, with relief after taking food or alkali, or following emesis is of no differential value, for it is frequently encountered in carcinoma as well as in benign ulcer.

5. A change in the nature of the distress is often considered important, but this occurs in both lesions.

6. Loss of appetite, loss of weight, loss of strength, coffee-ground emesis, melena, and anemia may occur in both conditions.

7. Gastric Analysis. Of paramount importance is the demonstration of free hydrochloric acid in the gastric secretion, for a diagnosis of chronic

benign ulcer is *not* acceptable in the presence of *continued proved* (*histamine*) *achlorhydria.* Carcinoma, on the other hand, may occur, as in the case described, in the presence of normal acid values (free hydrochloric acid with histamine to 106!). Large numbers of Opler-Boas bacilli and lactic acid in abnormal amounts are not seen in benign ulcer.

8. Stool Analysis. The continued absence of occult blood from the stool speaks strongly (but not positively!) for a benign ulcer whereas the continued presence of occult blood after two or three weeks of treatment speaks equally strongly for carcinoma.

9. Roentgenologic Manifestations. The various criteria in use for the roentgen-ray evaluation of a given ulcer crater are related chiefly to the location, size, and depth of the lesion and the mucosal pattern about it.

a. Ulcers of the greater curvature are almost always malignant. According to Eusterman and Balfour [8] there are, in the files of the Mayo Clinic, records of only four benign ulcers of the greater curvature. Matthews [9] reviewed the literature carefully in 1935 and found only 22 cases described in sufficient detail to warrant that diagnosis.

b. Ulcers of the prepyloric or antral region are likely to be malignant, but many of them are not. Pathologically, the antrum is the favorite site for the development of carcinoma. Konjetzny [10] found 82 per cent of the gastric carcinomas to involve the antrum. Graham [11] found that 94 per cent of the ulcers situated between the incisura and the pyloric vein were histologically malignant. Holmes and Hampton [12] considered the majority of these prepyloric ulcers to be malignant.

c. Size is of relatively little practical value in the differentiation. Small lesions may be carcinomatous (see figure 1), and many large craters are benign.[13]

d. Benign ulcers usually give the appearance of extending beyond the normal confines of the gastric lumen whereas carcinomatous craters do not. Exceptions, however, are not infrequent.

e. Tumefaction, appearing as a halo about an ulcer crater, may often be seen by the use of manual pressure in both benign and malignant lesions, due in the former to edema and inflammatory swelling, in the latter, to these factors plus neoplastic infiltration.

f. The meniscus sign of Carman,[14] consisting of an ulcer crater located beneath the level of the lesser curvature and demarcated by a zone of tumefaction appearing as a halo, almost invariably denotes carcinoma.

g. In benign ulcer the adjacent mucosal pattern is usually smooth except for folds radiating to the lesion. Such radiating folds may also be seen in carcinoma but they are usually less numerous. Parallel folds ending abruptly at the margin of the lesion are strongly suggestive of malignancy. In neoplasm the mucosal pattern about the crater may be coarsely nodular.

h. Benign craters are usually smooth or slightly irregular; malignant craters are often so, but *markedly irregular* or *ragged* craters are almost

always malignant, the irregularity being due to the nodules about the margins.

i. Under adequate therapy the benign ulcer crater diminishes rapidly in size.[15] Complete disappearance of the roentgenologic crater, in the light of our present knowledge and assuming the use of satisfactory technic, speaks *very, very strongly* in favor of a benign lesion.

10. Gastroscopic Appearance. In experienced hands the gastroscope is of great differential value indeed, but it is not infallible. Attention is called to the fact that although, in the case cited in detail in the beginning of this article, Schindler, in his gastroscopic diagnosis, wavered as to the type of infiltration present, he did not think it necessary to consider the possibility of a benign lesion. To the pathologist, Dr. Steiner, however, the ulcer appeared grossly benign. The difference in the antemortem and postmortem appearance may be due, as Schindler and Steiner suggest, to an antemortem stiffness of the mucosa produced by the marked fibrosis throughout the submucosa. The benign ulcer, according to Schindler,[16] is generally crater-like, rarely shallow; its floor is whitish yellow and not often brownish in color, although after an acute hemorrhage it may be dark red. Its edges are sharp, often partly undermined. The adjacent mucosa in early lesions is often normal; later there may be marked inflammation of the surrounding mucosa but rarely of the entire stomach. Converging folds occur. The carcinomatous ulcer, however, is characterized by less sharp edges so that the ulcer floor seems to blend with the mucosa. The floor is irregular and contains nodules, nodes, or ridges. It is occasionally whitish or yellowish in color but more frequently brown, brown-red, violet, gray or a dirty color. The malignant ulcer is usually elevated, appears to lie on a hill, and therein differs from the benign ulcer. The adjacent mucosa may be nodular. Schindler contends that it is easier to differentiate benign and malignant ulcer gastroscopically than in the gross appearance of the resected specimen because of the color nuances produced by the circulating blood and also perhaps because of the stiffening produced by the fibrous, submucosal infiltration.

It is clear that none of the criteria mentioned is pathognomonic of a benign lesion, unless it be the roentgenologically and gastroscopically *observed* and *proved, complete* healing of an ulcer. The epithelized scar adjacent to the ulcer, in the case described in detail in this article, might suggest that even proved healing does not completely disprove malignancy. Such a state of affairs, however, has yet to be demonstrated clinically. In spite of the lack of pathognomonic signs of benign ulcer, the accuracy of the clinical differentiation of the two lesions, if one weighs carefully all of the evidence, is, I believe, very high, but precise statistical figures cannot, as yet, be given. Individual factors of interpretation, of cases to be included or excluded, color all statistics on the subject.

The therapeutic implications of the foregoing considerations are debatable. The surgeon may find in them ample justification and indication for

advising immediate, subtotal gastrectomy in all cases of gastric ulcer. Bloomfield [17] concluded that the errors in differentiation do not exceed the mortality rate of resection—a conclusion I share but cannot prove. A further consideration is the fact that end results of gastric resection for carcinoma, even the so-called "early carcinomas," are not yet sufficiently impressive to warrant indiscriminate resection for benign ulcer. The practical plan of carefully following for a few weeks the lesions which appear to be benign is justifiable, and, I think, to be commended, provided the *course* of the lesion is actually studied. The particularly significant points to be observed are: (1) The disappearance and then the continued absence of occult blood from the stool, and (2) rapid diminution in the size of the crater as seen roentgenologically and gastroscopically. One can never rest content until the diagnosis of benign gastric ulcer is proved objectively by complete healing or by careful histologic examination. It is perhaps not necessary to add that patients with gross ulcers and histamine-achlorhydria, patients with ulcers of the greater curvature, and patients with questionable ulcers of the antrum should be promptly subjected to partial gastrectomy, for such lesions are usually malignant.

Conclusions

1. The existence of carcinomatous degeneration in benign ulcer remains to be proved conclusively.

2. Peptic ulceration of carcinoma may produce a lesion grossly indistinguishable from benign ulcer.

3. Although there is no pathognomonic sign to indicate the benign nature of a lesion, the total evidence available from careful study permits the clinical differentiation of benign and malignant gastric ulcer with a high degree of accuracy.

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THE POSTGRADUATE PORTION OF MEDICAL EDUCATION *

By C. Sidney Burwell, M.D., F.A.C.P., *Boston, Massachusetts*

The annual session of the American College of Physicians is an appropriate place to discuss this subject of medical education. These Fellows of the College are themselves all students; their purpose in attending this meeting is to study medicine; the meeting represents an important variety of medical education.

When our President honored me with his invitation to discuss the graduate phase of medical education, he in effect asked me this question: "What do you think about this problem?" My answer, such as it is, represents my own conclusion and is not to be taken as implicating any faculty, committee, or group.

First, medical education is a long business. Because it is long and involved, I propose to begin by outlining its general course and development as medical education is practiced in America. If one could only give a description of the stages of medical education as concise and clear as Osler's description of the stages of typhoid fever, the cause of understanding would certainly be aided.

Of course the whole educational process bears on the training of doctors. Our discussion may begin, however, with the college training that precedes admission to medical school. If we were actually talking about typhoid, we could discuss here the incubation period and the prodromal symptoms. As it is, we must use the phrase "pre-medical training." The functions of this period are at least two: to advance the liberal education which is the preparation for life, and to supply a ground work for subsequent professional activity. There is no reason to think that this preparation should be the same for all; there are many reasons for encouraging diversity of preparation and for keeping required work at a minimum. As the President of Harvard University pointed out at the meeting of the Council on Medical Education of the American Medical Association last month, the college courses of the pre-medical period should be selected by the student because they are of value in his education and development, and not because he hopes they will make a good impression on admission committees. There is a great opportunity for improving the effectiveness and diminishing the confusion of this period by consultation between college faculties and medical school faculties, but in the main the responsibility for the quality and content of pre-medical work belongs to the college. College faculties are concerned with the preservation of liberal education as well as with the development of pre-professional education and it is a good principle of administration to see that primary responsibility is clearly placed.

* Read at the New Orleans meeting of the American College of Physicians, March 27, 1939.

The second period of medical education is the basic four-year course in the medical school. This may be compared to Osler's " fastigium "—the height of the disease, the period of continued fever. This period appears, at least to teachers in medical schools, to be the indispensable center of medical training. As specialization develops, this basic training becomes not less but more important. The basic medical course is the doorway through which men pass to all the fields of medicine. It still constitutes the most powerful influence tending to unite the varied fields of medical work and to prevent the isolation of specialists—an isolation that may result in a dangerous tendency to deal with parts of problems and parts of patients. This central or basic training is altering rapidly under the impact of the advance of medicine. It is becoming, on the whole, *less vocational* and more basic, and this change will probably go further. Even now medical schools do not, in general, prepare their students to practice medicine to the same degree that they did 20 years ago. They do pretty well, in my opinion, if they supply a foundation on which subsequent vocational training and experience may be firmly based.

This point of view is widely accepted. Thirteen schools in the United States and four in Canada make an internship a prerequisite for the M.D., and 20 state boards (plus Alaska and the District of Columbia) require such an internship as a condition of licensure. Such a hospital period of intensive vocational experience, under direction, but with increasing responsibility, is accepted as an indispensable portion of medical education. It may be expected that more state boards, as the bodies responsible for setting up the conditions of licensure, will so regard it. I take it as clear that the internship and its organization is the responsibility of the hospital. If it offers a high standard of work, a professional staff interested in the development of doctors, and reasonably good food, it will be a good internship and good men will apply for it. The internship is so important that it may be compared with the " crisis " in the course of typhoid fever, defining that term as " that period of change which may determine whether the result is to be good or bad."

That seems to end my typhoid metaphor. I refuse to consider the practice of medicine as convalescence from medical school or to get entangled in any light conversation about immunity to further education.

We come now, after considering a period of nine or 10 years of hard but intensely interesting work, to the problem of further training. Here we encounter the fields of graduate and postgraduate training, the chief theme of this discussion. No one has expressed more clearly the definition of these fields than Bruce, who writes, " By the term ' postgraduate ' I refer to a program of teaching designed to maintain the practitioner at a suitable standard of professional fitness. By ' graduate ' is meant those longer courses of study designed to prepare for teaching, research, or practice of a specialty."

For our purpose today, a few words about " training designed to maintain the practitioner at a suitable standard of professional fitness " will suffice, important as this field of work is. Assuming a good basic training, such *postgraduate work* is arranged to maintain the practitioner at a suitable standard, to keep him abreast of a rapidly moving current, and to aid him in continuing his growth, but not to change his spots by making him a specialist. The methods of postgraduate training are many. For example, one of the functions of education in general and of medical education in particular is to encourage the formation of the habit of scholarship. Such a habit may manifest itself through attendance at medical meetings (such as this one), through the utilization of personal experience as a means of education, through the taking of formal, so-called *refresher* courses, or through incessant and intelligent reading. Certainly the habit itself is more important than the means of putting it into action. But these means are certainly not unimportant and one of the interesting developments of recent decades in American medicine is the long series of thoughtful and earnest efforts to improve the opportunities for this sort of work. Happily the profession itself has decided that it wants opportunities for postgraduate training and is intelligently and with energy setting them up. Many medical societies have played an important rôle, aided by hospitals, schools, and health departments. Many plans take into account particular problems of particular regions or groups. In short, there are many opportunities for keeping up and they appear in general to be in good hands.

It is with the other aspect of post-intern training that my thoughts are now primarily concerned—what Bruce calls " graduate training " and defines as " those longer courses of study designed to prepare for teaching, research, or practice of a specialty." The preparation of men for special forms of practice is the main theme of these paragraphs, but in general the principles suggested will apply as well to the preparation of men for teaching and research.

A very brief perusal of the history of medicine will reveal the great importance of specialization. Special knowledge and special skill have been important factors in the progress of medicine and in the elevation of the standards of medical care. As part of the movement to improve the standards of practice, there have during some 20 years been set up a dozen or so special examining boards—such as the American Board of Internal Medicine—which are prepared to certify as to the qualification of individuals to practice various specialties. A large number of young men are now concerned with satisfying the requirements of these boards. These requirements then will have a determining influence on the type of opportunity that will be sought as graduate work. It is on the relation of these requirements and these boards to the general problem of medical education that I wish to offer one or two timid meditations.

Meditation number one is concerned with the subject of specialization

in general. It will, I daresay, be agreed that specialization is essential to modern practice and to the advance of medicine. Nevertheless, like all potent drugs, it can produce symptoms of intoxication if used in too great an amount or too high a concentration. Not only may special groups become concerned with parts of people and lose touch with the wider problem of the whole patient, but such groups may actually become isolated and lose some essential contact with other fields. This may not be very serious for the first generation of specialists in a given field, but it might be really grave for their students or their students' students. This suggests to me the daring hypothesis that perhaps no group should be wholly responsible for the training of its own successors. Is it not one of the advantages of bi-sexual reproduction that sons do not in all respects resemble their fathers?

Let me cite an example of the undesirability of special groups training their own successors. The last 30 years (which is the time equivalent to a human generation and about the interval between influenza pandemics) has seen a great and on the whole useful development of laboratories of so-called clinical investigation. These, in the main, have been organized by men deeply concerned with the problems of disease in patients and bringing to attack those problems the methods of anatomy, physiology, chemistry, physics, pharmacology, pathology, bacteriology, and genetics. For all their expertness in the exploration of disease these men are not (there are rare exceptions) professionals in the fundamental medical sciences as well; therefore they want to see coming into their laboratories a stream of young men trained in the basic sciences of today and not of the time when you and I were young.

On the basis of such general ideas, I venture with great trepidation and all due respect (and very seriously) to suggest that all special boards should include representatives of the general fields of medicine and surgery and that boards of broader interests (such as the American Board of Internal Medicine) should include representatives from at least some of the important specialties. It has even occurred to me to wonder whether the training of internists would not benefit from the proximity and counsel of surgeons. And vice versa.

Such a wise and generous action would have another useful function. There are examples in the history of medicine which indicate that special fields may be more important as special fields at one time than at another, or that they may exist at one period in a different relation to the general field of medicine or to other special fields than at another time. New specialties will arise, some present ones will change their form, or be absorbed back into the central body of Medicine. Rigidity of classification is biologically undesirable. This simple scheme might help to avoid it.

My second meditation has to do with the type of educational opportunity which should be available to those who seek development as experts in special fields. In this connection I quote the first paragraph of Dr. Pechey's preface to his English translation of "The whole works of that excellent

practical physician, Dr. Thomas Sydenham"; it was written in 1695:

> "He that designs to attain to the right understanding of any Art or profession, usually chooses some Eminent Man of the Art to be his Guide and Pattern, by whose Directions and Example, joyned with a tolerable Capacity, and sufficient Diligence, he is and is deemed, at a stated Period, legally qualified for the Exercise of that Art he professes. And this I take to be the best and readiest way of attaining to the knowledge of any Art."

And I should agree with Dr. Pechey that so far as my experience with education goes, there is no substitute for working with competent leaders; the indispensable factors in this graduate phase of medical education are good men working in good hospitals. Dr. Halsted is quoted as having said once that the only important principle of making a medical school curriculum was to take the teaching away from the poor teachers and give it to the good ones.

Moreover it is a cause for rejoicing that many of the boards have recognized the importance of diversity of opportunity for men preparing for work in the same field. These boards wisely consider that they are primarily concerned with results, and the more originality and diversity the young men display in their approach to the special field, the better. There is another advantage to having the plan of training quite fluid; actually such elasticity is a protection to the ultimate standing of a given board. If a specific course of training is laid down it will certainly not be the best course for all men to follow. Not all independence and courage are dead, so that some men will follow their own ideas of training. Occasionally these may be very good, especially in rapidly changing types of practice. Under these circumstances we may be forced to recognize that some of the most effective people in a special field are not "properly" trained. In other words, success at state board examinations is not the ultimate test of medical education.

There are many other reasons for elasticity, freedom, and the avoidance of formal courses. One is that medical education has been entangled in overmuch conversation for many years. Students are just now escaping from the passive rôle of hearing many lectures into the more effective types of educational procedure in which they are active as well as the teacher. One of the dangers of a too formal development of graduate training is that there will be too much talking. This would be a backward, not a forward, step. Happily, the wisdom of medical men is such that most of the boards *are* concerned with competence, rather than with details of acquiring it.

Moreover, this general notion is in harmony with the astonishing breakdown of interdepartmental barriers that is now going on in teaching and research institutions. Investigation, instruction, and the care of patients are more often coöperative enterprises than they were. Even the archi-

tecture of newly built schools and hospitals reflects this significant change in point of view.

My third meditation (and the final one) is concerned with the responsibility for opportunity for graduate work in the various special fields. Whose business is it? Here, I think, the water is perhaps deeper, certainly it is harder to see the bottom. Some aspects of it may, however, be made out. The men who compose the specialty groups have a large part to play. These internists, surgeons, pediatricians, obstetricians, and others will assume, as members of the staffs of hospitals where such training is carried on, the chief responsibility for establishing the standards and turning the machinery of graduate medical training. They are the people who will actually carry on the teaching.

Equally clearly, the hospitals where such training is offered are deeply concerned with the plans for graduate teaching. These plans are bound to have an influence on the organization of services, the growth of the resident system, and the educational responsibility of the hospitals.

It doesn't seem to me important that training for specialties should be in connection with medical schools and university hospitals, although of course it often will be. We are considering a very high type of vocational training, and such training, in my opinion, is not the first responsibility of the university medical school. The main concern of the medical school should continue to be the provision of the basic four-year course on which the splendid superstructures of graduate training are to be founded. These schools should not be placed in a position where the demands of graduate training could lower the standard of the undergraduate opportunity, any more than so-called premedical work should be allowed to injure a student's general education in college. And finally the many branches of organized medicine, including the American Medical Association and its special sections, and many special societies, have a deep interest in and responsibility for graduate education. For example, the American Board of Internal Medicine is the joint concern of the Section on Medicine of the American Medical Association and of the American College of Physicians. The American College of Surgeons, as another example; has already assumed an important phase of the responsibility for the training of surgeons.

Indeed the responsibility for graduate training is perhaps in some danger because it is shared by so many groups. Hospitals and their staffs, medical organizations, the state, and the medical schools, are all concerned. Joint understanding and effort of these diverse groups are absolutely indispensable conditions of any success at all in such an enormously difficult undertaking as graduate medical education. There is a great opportunity for leadership in the pursuit of this understanding by such an organization as the American College of Physicians.

CASE REPORTS

TRANSIENT FUNCTIONAL A–V HEART BLOCK INDUCED BY THE SWALLOWING OF FOOD; CASE REPORT *

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This case of functional heart block is being reported because we believe this syndrome, and especially milder manifestations of it, may not be as uncommon as the few cases reported would lead one to believe. Instances of Adams-Stokes syndrome, due to overstimulation of the vagus and without apparent cardiac pathology, have been reported as early as 1875 by Thanhoffer [1] and in 1898 by Neuburger and Edinger,[2] and others. It was not until 1934, when Weiss and Ferris [3] reported their thoroughly studied cases of syncope of reflex vagal origin—which they aptly termed "Vago-Vagal Syndrome"—that the present generation of physicians was reminded of the possibilities of functional A–V heart block, partial or complete, and its clinical manifestations.

Our case is almost a prototype of the one reported by Iglauer and Schwartz,[4] and very similar to case 3 reported by Weiss and Ferris.[3] These cases differ from the other instances of vago-vagal syndrome in that there is not only an absence of signs and symptoms of organic cardiovascular disease, but also an absence of signs and symptoms of organic disease in that organ (in this case the esophagus) from which the afferent impulses arise to reflexly, through efferent routes, influence the function of the A–V bundle. Dilatation of the esophagus, used by Iglauer and Schwartz, seems in this case as well to have a beneficial effect.

Case Report

A. G., female, aged 58 years.

F. H.: Mother, aged 71 years, died of tuberculosis; father, 65 years, died of a cerebral hemorrhage; one brother, 49, died of cancer; four brothers are well.

P. H.: Measles in childhood. Sciatica at 25 years. Hemorrhoidectomy and removal of uterine fibroid in 1909. Menstruation at the age of 15 years; regular; no dysmenorrhea. Menopause at 45 years. Marital: married at 32 years; six pregnancies; first three pregnancies miscarried before three months; fourth, fifth and sixth pregnancies normal deliveries.

P. I.: In 1928 patient began complaining of a feeling of abdominal distention, gaseous eructations, and other vague symptoms; a diagnosis of a spastic colon was made. Soon after she noted difficulty in swallowing; she said "the food goes down to a certain point, it fills me up and I have to drink water to force the food down." Patient also became dizzy when eating. A Sippy régime was instituted and she felt moderately well except for occasional attacks of dizziness when eating solid foods. In 1934 the attacks of vertigo became more frequent; and in addition loss of con-

* Received for publication June 21, 1938.

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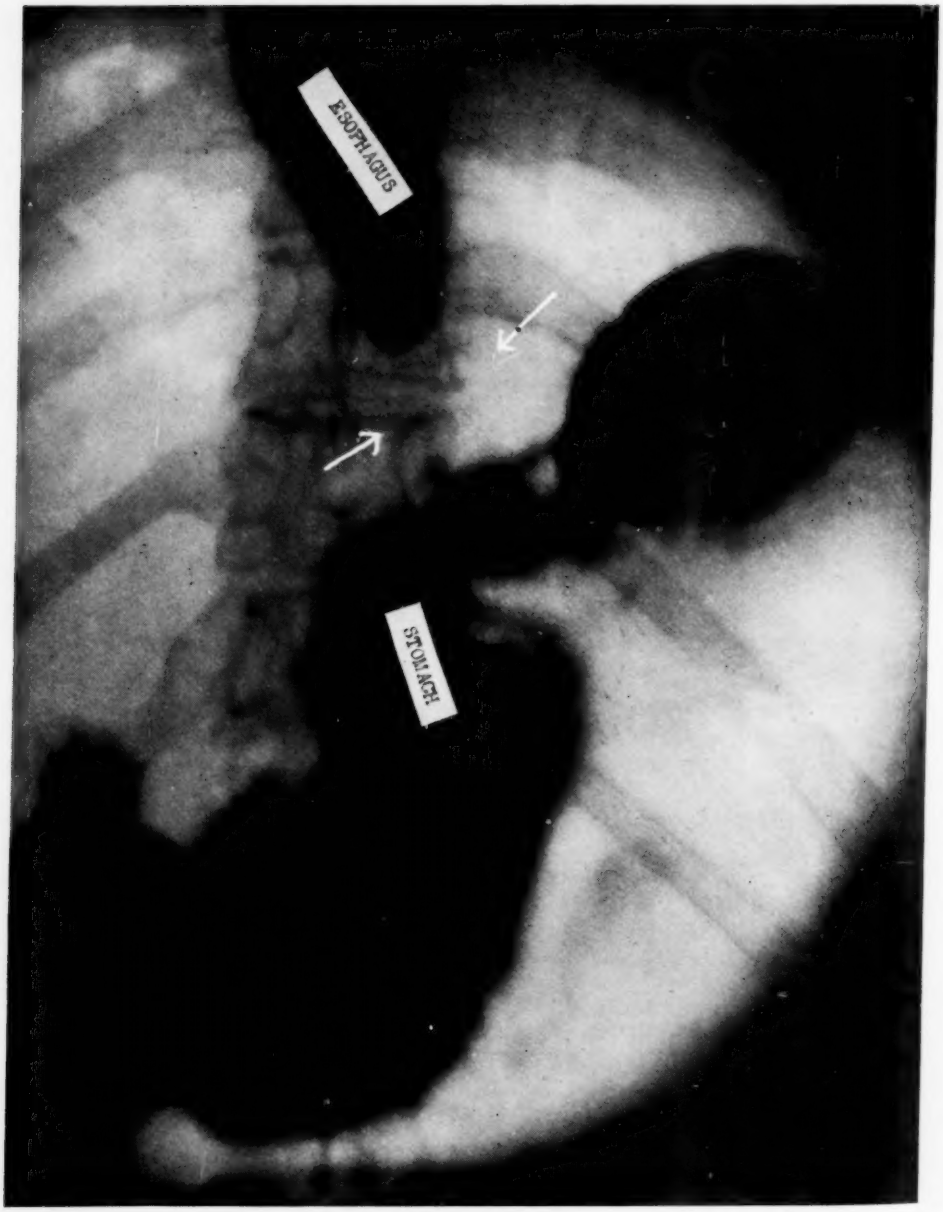


FIG. 1. Showing Cardiospasm.

sciousness for a few moments on swallowing would occur. Following this the patient would become frightened and excited, and her face, neck and upper chest would become flushed. These attacks now occurred after almost every meal and continued up to 1936 when patient came to our attention. She was admitted to the hospital for

esophagoscopy. Her chief complaints were difficulty in swallowing food, choking sensation, attacks of dizziness and faintness, and not infrequently loss of consciousness. This syndrome occurred only on the swallowing of food; between meals the patient felt well and was able to carry on without gastrointestinal, cerebral or cardiovascular symptoms. The bowels were regular; she slept well; there were no nocturnal attacks; and her weight varied with the severity of the symptoms.

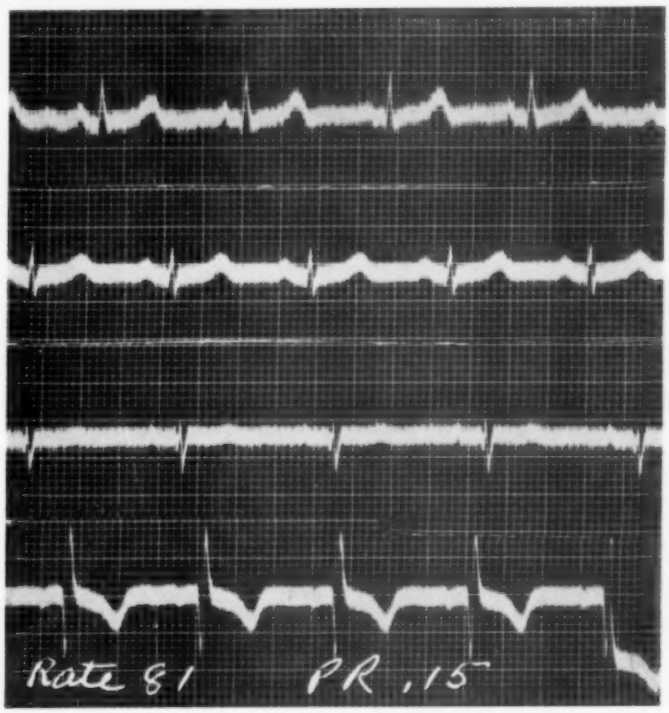


FIG. 2. Before eating.

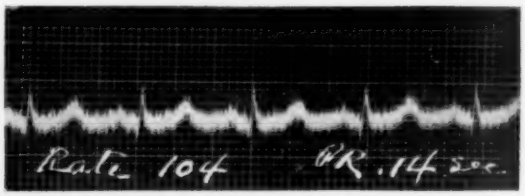
P. E.: Weight 122 lbs. Height 62½ ins. B. P. 140 systolic and 88 diastolic. Pupils react to light. Eye grounds negative. Small, scarred tonsils; small angular glands. No other lymphatic glandular abnormalities. No palpable thyroid abnormalities. Radial, brachial and temporal vessels soft; dorsalis pedis and posterior tibial vessels normal. Heart normal in size and shape; regular sinus rhythm; sounds of good quality; no adventitious sounds; second aortic sound slightly accentuated; ventricular rate between meals approximately 82. Carotid sinus pressure reaction negative, both sides. Lungs, abdomen and extremities negative. Reaction to exercise normal.

Fluoroscopy: The heart and its individual chambers appeared normal in size and shape in all fluoroscopic positions, and no abnormal positional relationship to its surrounding structures was noted. Pulsations normal. The aortic knob was commensurate with patient's age. Lungs and diaphragmatic movements were normal. The barium-filled esophagus was slightly displaced in its upper part by the aortic knob; it was dilated and the cardiac end was completely constricted to a spindle-shaped end (figure 1).

Electrocardiogram: Before eating (figure 2)—showed a regular sinus rhythm, ventricular rate 82. There are no T-wave or R–T interval disturbances; slight left

axis deviation; the P–R interval in the second lead is 0.14 of a second; and the chest lead (Wolferth application) showed no abnormalities.

Patient was then given a dry sandwich (meat and bread), and continuous electrocardiographic curves were taken in the first lead. All symptoms were noted and correlated in time on these records. Studies of these electrocardiograms show that while chewing food (figure 3A) her heart rate went to 100; no P–R interval changes were noted. After swallowing several times, patient complained that her food was sticking and at the same time developed a brassy cough (figure 3B). The heart rate



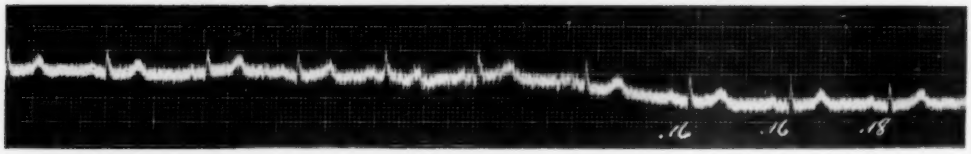


FIG. 3A (top). Chewing food before swallowing. FIG. 3B (below). Swallowing food; patient developed a brassy cough at this time. Ventricular rate now varied between 85 and 67; P–R intervals prolonged to 0.18 of a second.

dropped to 72; the P–R interval continued normal. The rate then became progressively slower and the A–V conduction time became 0.22 of a second, lengthened to 0.40 of a second, and then we noted a series of dropped beats; partial A–V 3:1 and 2:1 block. Patient complained of dizziness. She stopped eating; the rate slowly returned to 100 and the P–R interval to normal. This test was repeated several times with the same results (figure 4).

(The patient had not received belladonna or atropine for about two weeks before this examination. At no time during this examination did the patient become unconscious. She did become dizzy, faint and pale at times during these trials.)

Esophagoscopy: (Dr. Blumenfeld.) Cocaine 10 per cent solution; medium-sized Hesslinger esophagoscope. A constriction at the cricopharyngeus region of the esophagus was overcome by slight pressure. Another spastic obstruction was encountered at the region of the arch of the aorta. Below, the esophagus was ballooned out. The cardia was also found to be tetanic. The mucous membrane throughout was normal in appearance. No masses or other abnormalities were noted. *Impression:* Esophageal spasm. The examination caused no symptoms.

Laboratory Data: Urinalysis—specific gravity 1.018; slight trace of albumin; otherwise negative.

Blood—4,700,000 red blood cells; 75 per cent hemoglobin; 4,900 white blood cells; 60 per cent neutrophiles; 32 per cent small lymphocytes; 4 per cent large lymphocytes; 4 per cent eosinophiles.

Wassermann reaction negative.

Treatment and Interim History: It had already been noted that patient's symptoms were relieved by the administration of grain 1/100 atropine sulphate, t.i.d. For about two weeks before our studies, all medication had been discontinued and patient began again to experience the symptoms as described.

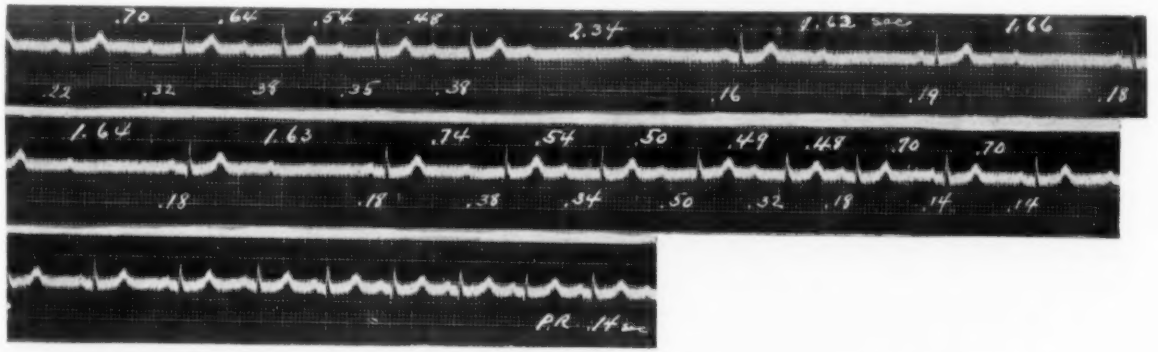


FIG. 4. Lead I—Continuation of figure 3. The numbers above the isoelectric line are the rest and recovery periods of the bundle; those below—P–R interval. The end of the second strip and the last strip, taken when patient had stopped eating.

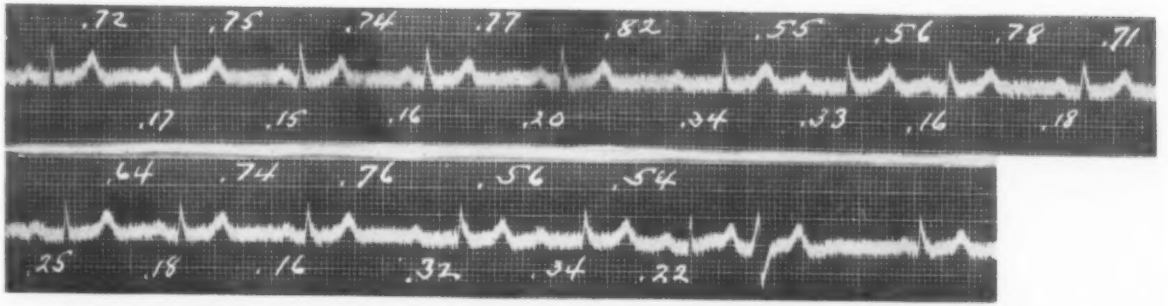


FIG. 5. Taken March 31, 1938—First Lead. Numbers above base line measure rest and recovery time of the bundle; numbers below, length of the P–R interval. Notice disproportion between length of rest and recovery time and the length of the P–R interval immediately following; notice also the sinus arrhythmia.

Subsequently the patient was given tincture of belladonna, minims 10, t.i.d., and esophageal dilatations, using a Hurst mercury filled esophageal dilator, 30 English, twice a week, were instituted. During the first week she had to coax her food along with sips of water; and while during the following two weeks she still encountered some difficulty in swallowing solid food, she experienced no difficulty with liquid and semi-solid foods. After the fourth week she had no more dizziness or syncopal attacks. The belladonna was then gradually reduced and finally discontinued; the esophageal dilatations were continued, but less frequently; no symptoms were produced by this procedure. Up to the present time patient has been comfortable and free from any sort of distress—without the administration of the atropine. During moments of excitement she may experience some difficulty in swallowing, but she has had no syncopal attacks for over a year.

On March 31, 1938, we repeated the examinations of 1936. Upon eating a sandwich patient experienced no symptoms and the electrocardiographic studies showed no change in rate or conduction time. When later she tried to swallow a thick bismuth meal, she complained "it could not go down." Upon fluoroscoping her we noted a cardiospasm of a lesser degree than had previously been observed. An electrocardiogram was taken while she was swallowing water to relieve her of the effects of the bismuth meal. This electrocardiogram, figure 5, showed a slowing of the cardiac rate, changes in conduction time, ventricular extrasystoles and subsequently a return to previous status.

Discussion

We feel that this is a case of transient functional A–V heart block because at no time did patient show any subjective or objective signs of organic cardiovascular disease. In heart block due wholly or partially to pathologic changes in the bundle, there seems to exist—in the partial A–V block with drop beats of the Wenckebach type—a definite relationship between the rest and recovery time of the bundle (measured from the beginning of the ventriculogram, "Q" or "R" wave, to the upstroke of the next conducted P-wave) and the immediately following A–V conduction interval; the shorter the rest and recovery time, the longer the conduction time and vice versa. In these curves, however, this relationship does not always exist. In figures 4 and 5 one can see many instances—after rest and recovery time of 0.82 of a second, conduction of 0.34 of a second; after a rest and recovery time of 0.56 of a second, conduction time of 0.16 of a second; after rest and recovery time of 0.74 of a second, 0.16 of a second; after 0.77 of a second, 0.20 of a second. This change in relationship seems to show that the functional capabilities of the bundle are constantly varying with changes in vagal tonus, regardless of rest and recovery time. Changes in rate do not always occur at the same time as changes in conduction—there may be a considerable slowing of the sinus rate with no P–R interval changes, and P–R interval changes can occur without a slowing of the sinus rate; i.e., the increased vagal tonus may manifest itself both in the slowing of the sinus activity—predominantly through the right vagus—and lengthening of the conduction time—predominantly through the left vagus—at different times and in different degrees. This, of course, speaks for a functional causation of these phenomena.

It was noticed that upon swallowing the patient developed a brassy cough, lasting for a short time, similar to that which one hears in recurrent laryngeal involvement. This shows, we believe, that other efferent pathways may be involved in this vago-vagal syndrome.

At no time during a two year period have we obtained evidences of organic disease in the esophagus or in any of the surrounding organs.

Summary

A case of transient functional A–V block, induced by swallowing of food has been presented. There are no evidences of organic disease. Dilatation of the esophagus seems to have a beneficial therapeutic effect in this type of case.

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RENAL INSUFFICIENCY WITH TETANY IN AN ADULT; REPORT OF A CASE*

By E. Perry McCullagh, M.D., F.A.C.P., and E. J. Ryan, M.D.,
Cleveland, Ohio

Case Report

The patient was a Jewish woman, 48 years of age. Her symptoms appeared in 1905 when she was 29 and in her second pregnancy. At that time, she had the first of a long series of attacks which were characterized primarily by weakness of the muscles of the extremities of such severity that she was unable to walk or to raise her hands or arms. These attacks, varying in severity but essentially similar in character, continued to occur in this form at irregular intervals of one to six months until six months before she came under our observation in 1937, at which time their character changed as will be described. She was relatively symptom-free between episodes. The attacks were seasonal in that they were much more likely to occur in the winter or spring months and were much less frequent in the summer or during visits in the South. A typical attack might run a course of three or four days, relief apparently being obtained by large doses of a mixture containing potassium citrate and sodium salicylate. The level of serum calcium in 1926 was 13.0 mg. (?) per 100 c.c., and of blood urea 45 mg. per 100 c.c. Physical examination revealed no findings of significance and no definite diagnosis was made.

For four years after her marriage at 22 years of age, she had failed to menstruate. During that time, her weight fell to 97 pounds. She also gave a history of some polyuria and nocturia over a period of years. In the light of our present knowledge, it appears that these symptoms may have been of renal origin. Physical examination in 1934 again revealed essentially normal findings. The blood pressure was 110 systolic, 70 diastolic. At no time during her illness was the blood pressure elevated and at no time did she have any edema. The erythrocyte count was 4,890,000

* Received for publication June 2, 1938.

with 94 per cent hemoglobin; the white count was 11,150 with 52 per cent neutrophiles, 1 per cent eosinophiles, 44 per cent lymphocytes, and 3 per cent monocytes. The urine showed a trace of albumin and many white cells. The level of the serum calcium was 8.24, the phosphorus 3.4, and the blood urea 39 mg. per 100 c.c. The basal metabolic rate was minus 8 per cent. Roentgen examination of the skull revealed no abnormalities. Examination of the eyegrounds showed a haziness of both optic discs, and mapping of the visual fields revealed a questionable defect in the left superior quadrant, but no change of diagnostic significance. Calcium lactate and large quantities of milk were prescribed and she was advised to take sunbaths. The flaccidity of the muscles during attacks at that time had spread to involve those of the neck as well as the extremities.

During the next several years, the levels of the serum calcium and phosphorus estimated at various intervals were sometimes normal but usually the calcium level was depressed and the phosphorus elevated. She continued to have attacks at somewhat less frequent intervals. Both the patient and her husband emphasized the fact that these attacks were those of muscular flaccidity, an observation borne out by the report of a physician who examined her at home during an attack in 1935. He reported muscular flaccidity, affecting particularly the neck and extremities and negative Chvostek's and Trousseau's signs. At that time, 15 c.c. of a 10 per cent solution of calcium gluconate intravenously did not relieve her.

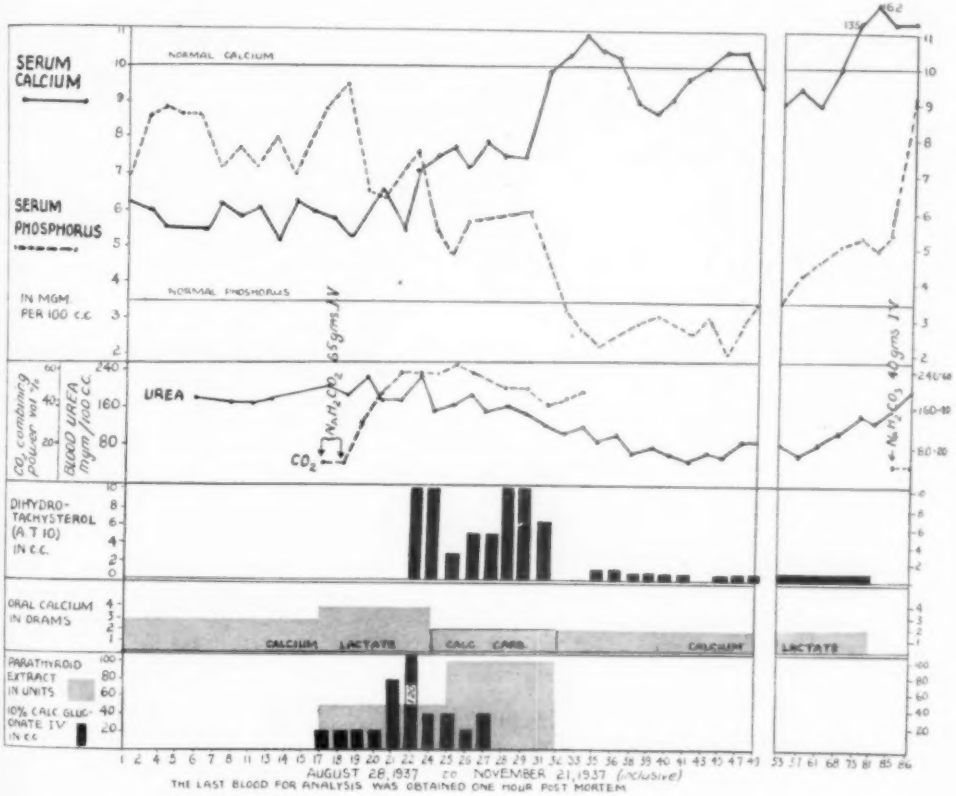
In the spring of 1937, the attacks began to assume the character of true tetany; there was carpopedal spasm as well as spasm of the neck, back, and leg muscles. Spasm of the muscles of the jaw was so marked that she could not open her mouth. Trousseau's and Chvostek's signs became positive.

She was admitted to the hospital on August 28, 1937, with fairly characteristic tetany attacks. The level of serum calcium was 6.2 mg., phosphorus 6.8 mg., and blood urea 180 mg. per 100 c.c. The urea clearance test showed 10 per cent clearance at the end of the first hour and 13 per cent at the end of the second. This was the first time significant evidence of kidney damage had been demonstrated. There was no steatorrhea. The erythrocyte count at that time was 4,520,000, with 81 per cent hemoglobin; the leukocyte count was 10,550, with 76 per cent polynuclears. The urine showed a strongly acid reaction, a faint trace of albumin, and was loaded with white cells. Roentgen studies of the skeleton showed no decalcification of the spine, ribs, or pelvis. Some improvement followed administration of vitamin D, parathyroid extract and calcium gluconate intravenously, and she was dismissed on September 4, 1937, 50,000 units of vitamin D being given daily.

Her course during the ensuing 9 days was progressively downhill, and she was readmitted to the hospital on September 13, 1937, apparently in a dying condition. She was semicomatose. the skin was flushed, and the respirations hyperpneic in character. Urea frost was present during the next few days. The level of serum calcium was 5.9 mg., phosphorus 8.9 mg. per 100 c.c., blood urea 207 mg. per 100 c.c., nonprotein nitrogen, 123.2 mg. per 100 c.c., and carbon dioxide combining power 9.9 volumes per cent. A specimen of urine secured by catheterization on September 15 showed one plus albumin and it was loaded with white cells. Examination of the blood on September 21 showed 2,880,000 red cells with 58 per cent hemoglobin and 16,450 white cells with 83 per cent polymorphonuclears.

The important blood chemical findings from August 28 to November 21, the day of her death, may be traced on the accompanying chart. The days numbered 17 to 49 inclusive cover the period of this hospitalization. The output of urine was consistently high, varying as a rule between 2000 and 3000 c.c. per day with a relatively fixed specific gravity, the morning specimen never falling below 1.007 and never rising above 1.014. Her immediate danger was the severe acidosis which was successfully overcome by the intravenous administration of 65 grams of sodium bicarbonate (5 per cent solution) in two days. The tetany was treated first by parathyroid extract

given in doses of 50 units per day from the seventeenth to the twenty-fifth day and 100 units daily from the twenty-fifth to the thirty-second day. Calcium gluconate in 10 per cent solution was given in amounts varying from 20 to 120 c.c. daily from the seventeenth to the twenty-seventh day. These were followed by only a slight shift in calcium and phosphorus levels. Dihydrotachysterol (A.T.–10) * was started on September 18, following which there was a striking return of the serum calcium and phosphorus to normal levels, as may be seen on the chart. Coincident with the improvement in serum calcium and phosphorus levels, the blood urea fell, being 68 on the day of dismissal from hospital (day 49 on the chart). A part of the improvement was judged to be due to glucose solution given intravenously each day and to



two blood transfusions. Cultures of the urine made shortly after admission showed *Bacillus proteus* on three occasions; all others showed *Bacillus coli* only. Urinary antiseptics included 20 c.c. of salihexin and 110 c.c. of prontosil. There was some improvement in the urine but small amounts of albumin and some pus were persistently present. The erythrocyte count and hemoglobin were only slightly increased. Urea clearance on dismissal was 19 per cent at the end of both the first and second hours. The improvement in blood chemistry was strikingly manifested by clinical improvement, and she was discharged on October 16. Doses of 2 c.c. of A.T.–10 were prescribed every second day and calcium lactate was given in doses of one-half a dram four times daily.

* A.T.—10 is a 0.5 per cent solution of dihydrotachysterol ($C_{28}H_{46}O$) in oil of sesame. (Winthrop Chemical Co.)

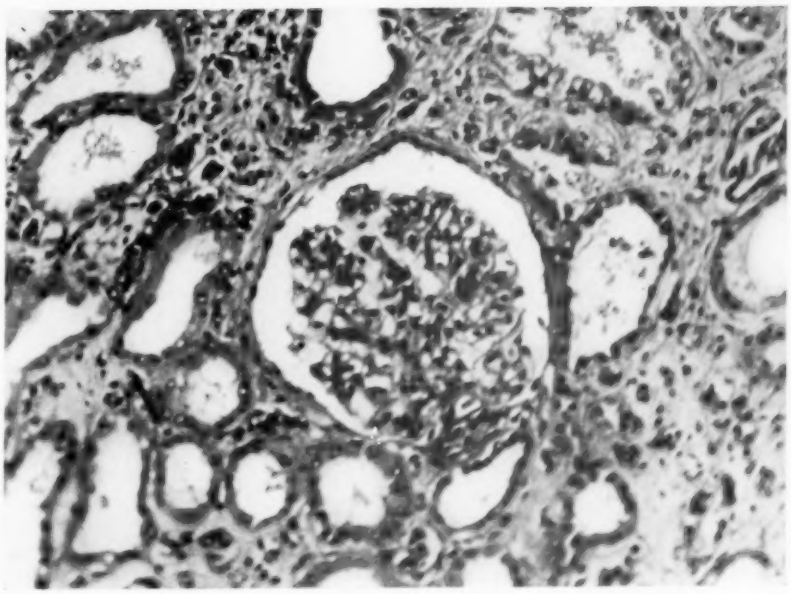
The patient remained under observation at home from October 16 to November 20. During this time, although ambulatory, she rested a great part of each day and was extremely pale and weak. She had no further attacks of tetany. The levels of serum calcium and phosphorus were checked at intervals of four days to a week and remained essentially normal until November 16, when the calcium was found to be 16.2 mg. per 100 c.c. The use of dihydrotachysterol was discontinued at once. The blood urea gradually rose and on November 16 was 126 mg. per 100 c.c. An intravenous urogram made on this day showed no function of either kidney. She became progressively weaker during the ensuing four days and was again admitted to the hospital on November 20, 1937. At that time she was prostrated, her face was flushed, respirations were labored and hyperpneic, there was generalized muscular aching and tenderness. On admission, the carbon dioxide combining power was 10.9 volumes per cent, the blood urea 165 mg. per 100 c.c., and serum calcium 13.1 mg. per 100 c.c. The erythrocyte count was 4,040,000, hemoglobin 65 per cent and leukocyte count 15,700. The urine showed a trace of albumin and an occasional pus cell. She was given a total of 40 grams of sodium bicarbonate (5 per cent solution) and 1,000 c.c. of 10 per cent glucose in distilled water intravenously that evening. In spite of this, agonizing muscular pain developed which was only partially relieved by large doses of morphine, her temperature rose to 104° F. during the night, she sank into coma, and died early the following morning. In blood drawn about one hour post mortem, the urea was found to be 186 mg. per 100 c.c., serum calcium 13.0 mg. per 100 c.c., phosphorus 8.6 mg. per 100 c.c., and carbon dioxide combining power 10.9 volumes per cent.

At autopsy, the only significant findings were in the kidneys. The parathyroid glands were normal. The right superior parathyroid weighed 30 mg., the right inferior 60 mg., the left superior 55 mg., the left inferior 50 mg. There were no deformities of the urinary tract such as are so frequently seen in renal rickets of childhood. The following is a report by Dr. Allen Graham of the gross and microscopic renal pathology, the latter illustrated in the accompanying photomicrographs (figures 1 and 2).

"The right kidney weighs 115 gm. and the left 132 gm. Both are slightly smaller than normal and are covered by a thin capsule which strips fairly easily without tearing, leaving a fairly smooth surface, diffusely studded with minute white opaque areas. There are also diffuse, small cortical cysts in each kidney. Both kidneys cut with increased resistance. The cut surfaces are bulging and glistening. There is atrophy of the cortex throughout, and all the pyramids are considerably enlarged relatively and actually, and have a homogeneous, bluish white appearance. The papillae are considerably enlarged, somewhat edematous, but not ulcerated. There are a number of cysts involving the pyramids and the cortex, varying from 0.5 to 1.5 cm. in diameter. The calices, pelves, and ureters appear normal. There is a usual amount of peripelvic fat, which is not indurated. There is only a mild degree of atherosclerosis of the renal vessels." Postmortem cultures from both kidneys were negative and from both kidney pelves showed *Bacillus coli.*

Microscopic. "Sections from both kidneys show well marked arteriolar and glomerular sclerosis, extensive atrophy and degeneration of tubular epithelium, with considerable diffuse fibrosis in the cortex and very marked fibrosis in the pyramids. Many of the less affected tubules are considerably dilated. There are numerous areas of scarring in the cortex and considerable round cell infiltration in some areas. The large branches of the renal arteries show very little arteriosclerosis." (Figures 1 and 2.)

The pathologic diagnosis was, "bilateral, advanced, arteriolar nephrosclerosis, and chronic pyelonephritis."



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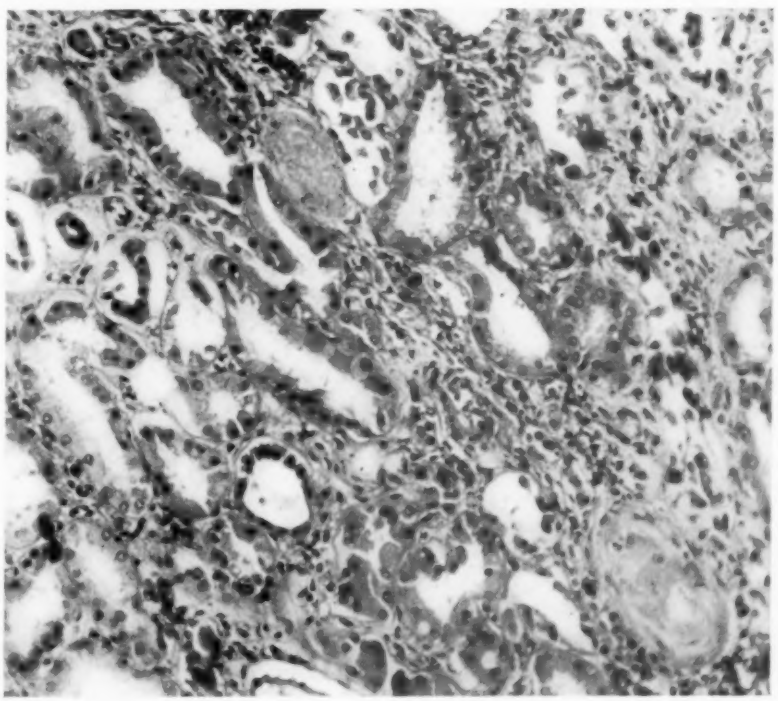
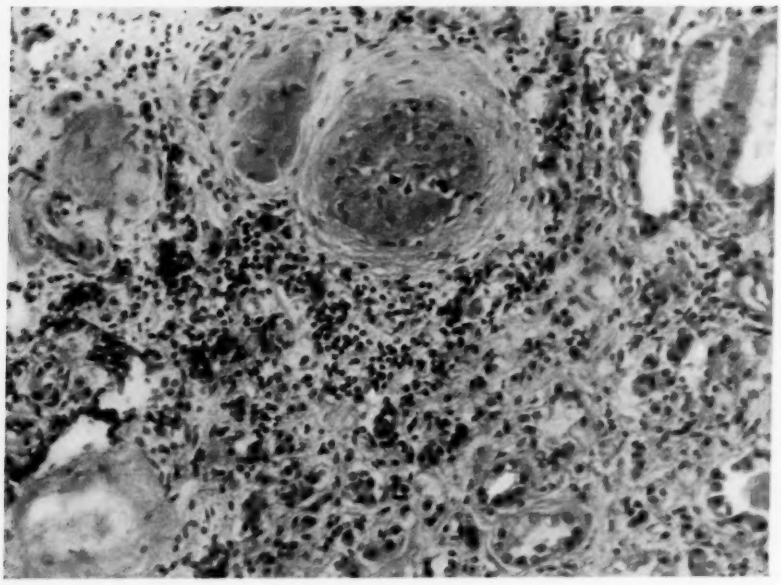


B

FIG. 1. *A*. Relatively unaffected glomerulus (× 150). *B*. Degenerative changes in the convoluted tubules (× 150).



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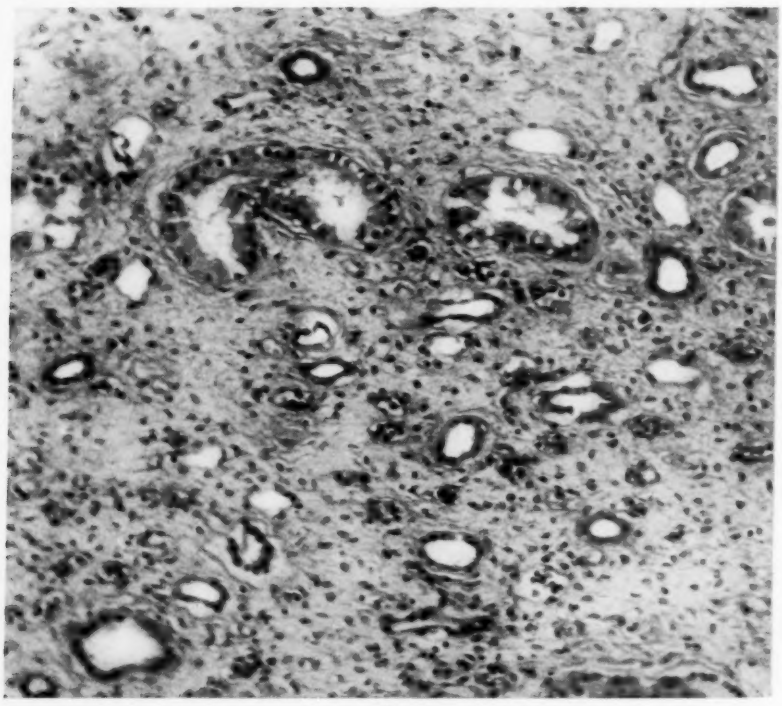

B

FIG. 2. *A*. Marked degree of arteriosclerosis, atrophy and fibrosis of parenchyma (× 150). *B*. Extensive fibrosis of medulla with atrophy of tubules (× 150).

Comment

This case is presented because of the rarity of tetany of renal origin in adults. It evidently simulates closely the changes seen with renal rickets in children. Spells of muscular flaccidity preceded signs of severe renal insufficiency by many years. Symptoms and signs typical of tetany appeared one and one-half years before death. The relative absence of urinary evidence of renal damage is consistent with the type of chronic pyelonephritis demonstrated and the complete absence of arterial hypertension is an interesting feature. No decalcification of the skeleton and no parathyroid abnormalities were recognized. The behavior of the serum calcium and phosphorus under the influence of dihydrotachysterol is demonstrated. The marked rise in the level of the serum calcium and fall of blood phosphorus, since they were persistent, could not be accounted for on the basis of intravenous calcium or parathyroid extract given. These levels had not responded to oral calcium therapy previously and were therefore due to the action of dihydrotachysterol. The lag between the time of first administration and the shift in serum calcium and phosphorus levels as well as the cumulative effect is typical of this drug.

APLASTIC ANEMIA TREATED WITH DAILY TRANSFUSIONS AND INTRAVENOUS MARROW; CASE REPORT*

By Edwin E. Osgood, M.D., Mathew C. Riddle, M.D., and Thomas J. Mathews, M.D., *Portland, Oregon*

This case is of interest for several reasons. The disease is uncommon. This patient received 43 transfusions totaling almost 22 liters of blood in 52 days. This prolonged life but produced polycythemia and enlargement of the spleen. Despite the amount of blood transfused the leukocyte and platelet counts remained at a relatively low level. No record was found of so large an amount of blood being given within this space of time.

Case Report

A white school girl, 19 years of age, entered Multnomah County Hospital on October 26, 1937, complaining of weakness, pallor, shortness of breath, and bleeding from the gums.

She had fibrocaseous tuberculosis of the apex of the right upper lobe since 1925. In 1931 she was treated for pleural effusion. She never had hemoptysis, cavitation, or tubercle bacilli in the sputum. She was found to be clinically well on examination at regular intervals from 1933 until about September 1937, when she first noticed dyspnea on exertion, pallor, and a throbbing sensation in her head. Her physician † gave her iron and liver extract and made the blood examinations recorded in table 1. On October 26, she first noticed slight bleeding from a spot on the gums near the left upper molars and black stools. She was sent then into Multnomah County Hospital.

* Received for publication August 27, 1938.

From the Department of Medicine, University of Oregon Medical School, and Multnomah County Hospital, Portland, Ore.

† The information on the illness from 1925 to Oct. 26, 1937, including the information in table 1, was kindly supplied by Dr. Ralph C. Matson of Portland, Oregon.

TABLE I

Blood Examinations Prior to Admission to Multnomah County Hospital

Date	Hemoglobin		R.B.C. millions per cu. mm.	W.B.C. per cu. mm.
	%	grams		
3/ 8/37.....	109	15.04	4.49	
10/ 4/37.....	39	5.38	2.55	
10/14/37.....	38	5.24	1.71	5,100
10/16/37.....	32	4.42	1.10	4,500
10/20/37.....	31	4.28	1.30	2,550
10/22/37.....	25	3.45	1.06	1,800
10/25/37.....	10	1.38	0.68	2,250

Careful questioning revealed no history of exposure to benzol, aminopyrine, arsphenamine, or other drugs containing the benzol ring. No exposure to radioactive substances was discovered. Between September 1931, and August 1937, she had 32 roentgenograms of the chest, and from October 13, 1933, until May 7, 1934, she had 59 five c.c. intravenous injections of gadusan, a preparation containing copper morrhuate. From May 9, 1934, to January 8, 1935, she was given 22 injections, intramuscularly, of oleosanocrysin which is gold sodium thiosulphate in oil. The individual injections varied from 0.1 to 0.5 gram, and totalled 5.4 grams.

Physical examination revealed a well nourished, well developed girl of asthenic habitus with an extreme white pallor. The temperature was 99.2° F. (37.3° C.), the pulse 130, and the respiration 22. The blood pressure was 110 systolic and 60 diastolic. The mucous membranes of the conjunctiva and mouth were almost white. There was one small bleeding point on the gums. Several fresh hemorrhages were noted in the retina of each eye near the disc. There were two small petechiae on the palate. There was slightly impaired resonance over the right apex but no râles or alterations in breath tones. There was no sternal tenderness, and the spleen, liver and lymph nodes were not enlarged to palpation. The fingernails were somewhat atrophic, but there was no spooning.

Laboratory studies established the diagnosis. The results of the blood examinations are given in tables 1 and 2. Table 3 * gives the nearest equivalent to the terms here used for the cells of the granulocyte and erythrocyte series. Urobilinogen was absent from the urine, and one plus albuminuria was noted on one or two occasions. A sternal puncture on the day of admission revealed hemoglobin,[1] 13 per cent (1.80 grams); akaryocytes, 0.44 million per cubic millimeter; nucleated cells, 725 per cubic millimeter; color index, 1.33; neutrophile lobocytes, 10 per cent; neutrophile rhabdocytes, 9 per cent; neutrophile metagranulocytes, 1.5 per cent; neutrophile granulocytes, 4.0 per cent; progranulocytes, 0.5 per cent; lymphocytes, 45 per cent; monocytes, 0.5 per cent; metakaryocytes and karyocytes, 27 per cent; karyoblasts, 0.5 per cent; disintegrating cells, 2.0 per cent.

The differential diagnosis, prior to the sternal puncture, included aplastic anemia, acute leukemia, and pernicious anemia. The sternal marrow findings definitely established the diagnosis of aplastic anemia with extreme normocytic anemia, thrombopenia, and leukopenia.

Pentose nucleotide, liver extract, blood transfusions, sodium perborate mouth wash, and intravenous sternal marrow injection were used therapeutically. The diet was high in protein with added brewer's yeast, viosterol, and orange juice to

* For the exact meaning of the terminology used here, consult OSGOOD, E. E., and ASHWORTH, CLARICE M.: Atlas of hematology, 1937, J. W. Stacey, Inc., San Francisco.

TABLE II

Transfusions and Results of Blood Examinations

Date	Amt. of transfusion, c.c.	R.B.C. million per c.c.	Hb. grams	W.B.C. per cu. mm.	Reticulocytes	N. Lobocytes, %	Lymphocytes, %	Platelets	Hemorrhage
10/26/37		0.94	3.48	3,800	1.0	27	63	16,000	++
10/27/37	550								
10/28/37	250								
10/29/37	500								
10/30/37	600	1.05	3.04	1,150	1.0	51	43	50,000	
10/31/37	500	1.50		1,000					
11/ 1/37	500	2.62	5.58	3,300	0.4	21	64	42,000	
11/ 2/37	600	3.20	8.13	3,900	1.4	14	74	140,000	
11/ 3/37	500								
11/ 4/37	500								
11/ 5/37	550	3.90	11.17	2,850	0.2	16	78	42,000	
11/ 6/37									
11/ 7/37	500								
11/ 8/37									
11/ 9/37	500	4.50	12.28	2,950	0.6	30	64		
11/10/37									
11/11/37	250								
11/12/37									
11/13/37	800	5.18	12.04	3,950	0.8	65	28	128,000	
11/14/37									
11/15/37		5.36	14.44	1,550	0.2	40	54	36,000	
11/16/37									++
11/17/37		5.06	15.97	1,550	N.F.	65	29	44,000	++
11/18/37									++++
11/19/37	500			1,000	N.F.	0	100	74,000	++++
11/20/37	600			1,250		20	80		++++
11/21/37	350	5.63	15.01	2,550		0	94		++++
11/22/37	600	4.45	12.70	750	N.F.	8	92	48,000	++++
11/22/37		4.35	12.09	1,400				20,000	++++
11/23/37	550	4.26	12.36	550	1.0	12	83	20,000	
11/24/37	500	4.57	12.86	850		6	92		
11/25/37	600								
11/26/37	500								
11/27/37	600	5.60	16.42	1,250	0.6	8	82	56,000	
11/28/37	600								++
11/29/37	500	5.10	15.57	1,750	N.F.	2	98	18,000	+++
11/30/37	500	5.35	17.49	1,650	N.F.	4	92	90,000	+++
12/ 1/37	350	5.44	16.12	1,150	0.8	8	92	42,000	+++
12/ 2/37	500								+++
12/ 3/37	500	5.81	17.47	1,050	0.6	24	72	36,000	+++
12/ 4/37	100								+++
12/ 5/37	575								+++
12/ 6/37	650 (−750)	8.11	18.00	280	0.2	6	84	112,000	+++
12/ 7/37	500	5.70	15.69	230	N.F.	0	94	96,000	+++
12/ 8/37	600	5.05	13.04	1,100	N.F.	6	90	58,000	++++
12/ 9/37	400	5.42	14.25	1,550	0.6	2	94	124,000	++++
12/10/37	600	5.08	11.73	1,050				90,000	++++
12/11/37	500								++++
12/12/37	500								++++
12/13/37	575+18 c.c. sternal marrow								++++
12/14/37	500	5.13	11.87	1,000		0	98	56,000	++++
12/15/37	500	4.45	10.91	750		0	98	50,000	++++
12/16/37	600	4.50	10.91	300		4	96	68,000	++++
12/17/37	420	3.80	9.66	250		8	80	70,000	++++

TABLE III

Nomenclature

Terms here used	Nearest equivalent
Lobocyte	Polymorphonuclear
Rhabdocyte	Staff cell
Metagranulocyte	Metamyelocyte
Granulocyte	Myelocyte
Progranulocyte	Promyelocyte
Granuloblast	Myeloblast
Akaryocyte	Non-nucleated erythrocyte
Metakaryocyte	Normoblast
Karyocyte	Pronormoblast
Prokaryocyte	Erythroblast
Karyoblast	Megaloblast

insure an adequate vitamin intake. Pentose nucleotide was given in 10 c.c. doses, intramuscularly, twice daily on October 27 and 28. Unconcentrated liver extract was given intramuscularly in doses of 3 c.c. twice a week until November 18. Sodium perborate mouth wash was used at frequent intervals, and sodium perborate paste was applied to the gums following meals. As shown in table 2, a total of 43 transfusions and 21,870 c.c. of blood were given by the citrate method. On December 13, 18 c.c. of sternal marrow were obtained from her brother, a compatible donor. This was introduced into marrow culture medium,[2] thoroughly mixed, added to 500 c.c. of blood obtained from the same donor, and injected slowly intravenously. No reaction occurred.

At first the course of her illness was surprisingly favorable. The bleeding ceased after the first transfusion and did not recur until November 16. The course of the temperature, pulse, and respiration are shown in chart 1, and of the blood examinations in table 2. She was afebrile, except for a slight elevation of the temperature after the second, third and fifth transfusions, until November 13 when she contracted a typical acute follicular tonsillitis from another patient. There was no evidence of gangrenous stomatitis. The follicular tonsillitis had cleared up by November 20, but fever persisted and became continuous in character after November 18. Bleeding occurred as indicated in table 2. On November 24, an abscess on the right buttock was discovered at the site of injection of liver extract which later became fluctuant and was drained. *Staphylococcus aureus* was recovered from the pus. A second sternal puncture on November 23 revealed hemoglobin, 110.0 per cent (15.32 grams); red blood cells, 4.36 million; nucleated cells, 1,150; neutrophile lobocytes, 8.4 per cent; neutrophile rhabdocytes, 0.4 per cent; lymphocytes, 83.6 per cent; prolymphocytes, 0.4 per cent; eosinophile lobocytes, 0.8 per cent; monocytes, 0.4 per cent; disintegrated cells, 6.0 per cent. By December 6, the red cell count exceeded 8 million. Since the leukocyte count was only 280, 750 c.c. of blood were withdrawn from her vein to allow further transfusion. From December 7 on, the increased fever and pulse rate, and the increasing dyspnea and cyanosis without other apparent cause led to consideration of miliary tuberculosis. Blood cultures were negative. By December 15, the cyanosis was extreme. The patient developed jaundice which was apparently of hematogenous origin. She died December 18.

The final diagnosis was normocytic anemia "corrected"; leukopenia and thrombopenia from complete aplasia of the bone marrow of undetermined etiology; multiple hemorrhages into the viscera and from the mucous membranes; terminal bronchopneumonia; old healed fibroid tuberculosis of the right upper lobe and apex of the left lower lobe; possible miliary tuberculosis of pulmonary type; splenomegaly with evidence of blood destruction; generalized icterus of hematogenous origin; staphylococcus abscess of the right buttock.

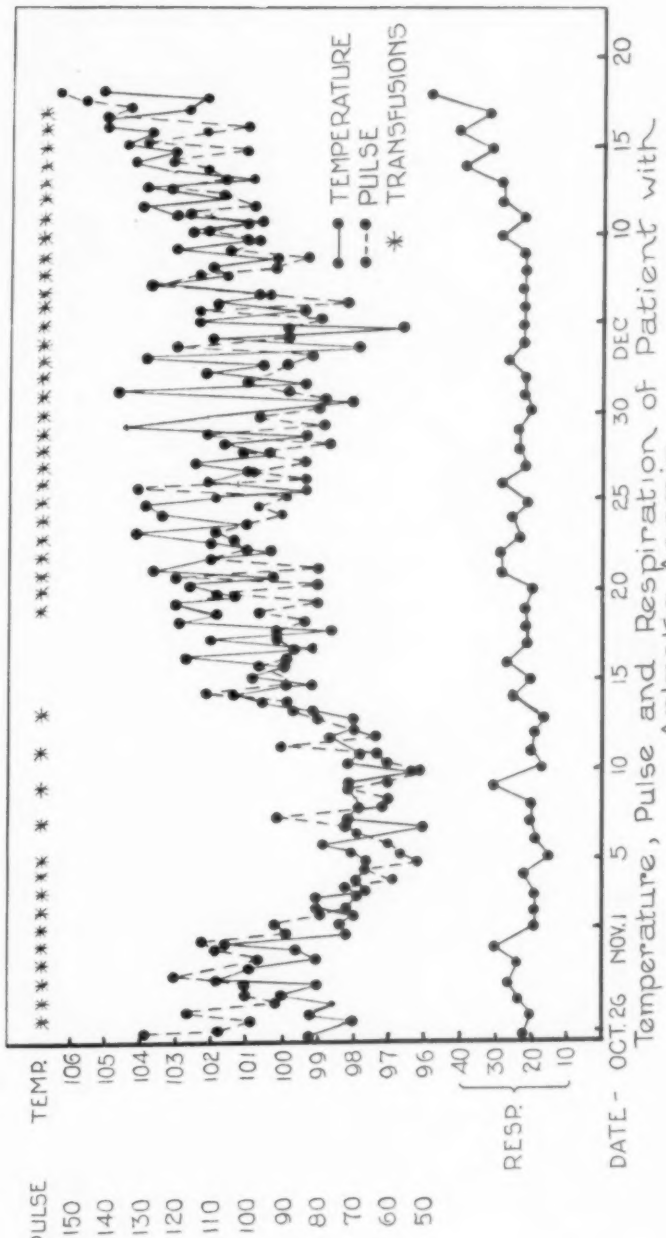
PULSE
TEMP.
RESP.
DATE - OCT. 26 NOV. 1 5 10 15 20 25 30 DEC 10 15 20
TEMPERATURE
PULSE
TRANSFUSIONS
Temperature, Pulse and Respiration of Patient with Aplastic Anemia

CHART 1.

Necropsy: Necropsy was performed * on the day of her death. The abscess on the buttock was healed, but a decubitus ulcer, measuring 3 by 2 cm., was present over the sacral promontory. The significant findings aside from petechiae in the serous membranes were in the marrow, lungs, spleen, and liver. There was no enlargement of the superficial or deep lymph nodes. Grossly, the ribs, sternum, and vertebral bodies revealed a markedly porous appearance with almost complete absence of marrow. The visceral and parietal pleura of the right lung were adherent by dense fibrous adhesions. On section the right lung was markedly bloody, consolidated, heavy and devoid of air. The section of the left lung revealed a dependent hypostasis with consolidation. The spleen was markedly enlarged, weighing 450 grams and measuring 17 centimeters in length, 10 centimeters in breadth, and 6 centimeters in thickness. The capsule was thick and grayish-black in color. The cut surface was bloody in appearance, purple to black in color, and had a fairly thin pulp. The liver was large, weighing 1,800 grams and showed petechiae beneath the capsule.

Microscopic examination of these tissues revealed findings of great interest. The marrow (figure 1) consisted largely of fat, but occasional islets of regenerating marrow which appeared essentially normal were visible. Sections from the apex of the right lung revealed extensive areas of fibrosis, infiltrated with focal collections of lymphocytes. There was a single large area of caseation necrosis surrounded by intact epithelioid cells and lymphocytes and an adjacent small active "daughter tubercle." Most of the substance of the lung in this region was made up of dense scar tissue. Many of the alveoli contained large numbers of monocytes filled with hemosiderin. There was extensive intra-alveolar hemorrhage. Sections of cut parts of the lungs revealed a patchy pneumonia which had become organized. The exudate contained monocytes and fibroblasts but no neutrophiles. In most sections of both lungs, thrombi were noted within the pulmonary vessels which were partially organized, and contained large clumps of cocci, some in chains and others diplococci. In some areas the bacteria were found in the surrounding parenchyma as well as within the vessels. There was no cellular reaction about these clumps of bacteria. No organisms were noted in any other tissue except the lungs. Sections of the spleen revealed large amounts of blood pigment. There was a good deal of phagocytosis of this pigment but no evidence of hematopoietic activity. Very few leukocytes were present. In sections of the liver the Küpfer cells contained large amounts of hemosiderin.

The anatomic diagnosis was terminal bronchopneumonia, bilateral, with multiple bacterial emboli in the pulmonary arterioles; aplastic anemia; hemorrhages into pelves of the kidneys, the mucosa of the stomach, and beneath the capsules of the kidneys and liver; hypoplastic bone marrow; old healed fibroid tuberculosis, right lung; generalized icterus; chronic passive congestion of the spleen and kidneys; splenomegaly; chronic fibrous obliterative pleuritis, complete, right lung; cystic endocervicitis; decubitus ulcer; hematomata in both cubital fossae of the arms.

Comment

The etiology of the aplastic anemia in this case is not definitely established, although the patient had been exposed to two known causes of this disease, gamma radiation [3] and gold sodium thiosulphate.[4] Since the chest roentgenograms were taken over a period of seven years, it does not seem possible that this small amount of radiation could account for her illness. Aplastic anemia has been produced by smaller amounts of gold preparations than she received. It seems unlikely, however, that it was the cause in this case because the last dose of gold was given in 1935, more than 19 months before the onset of the

* Drs. Warren C. Hunter and Bernard F. Ryan of the Pathology Department of the University of Oregon Medical School performed the necropsy.

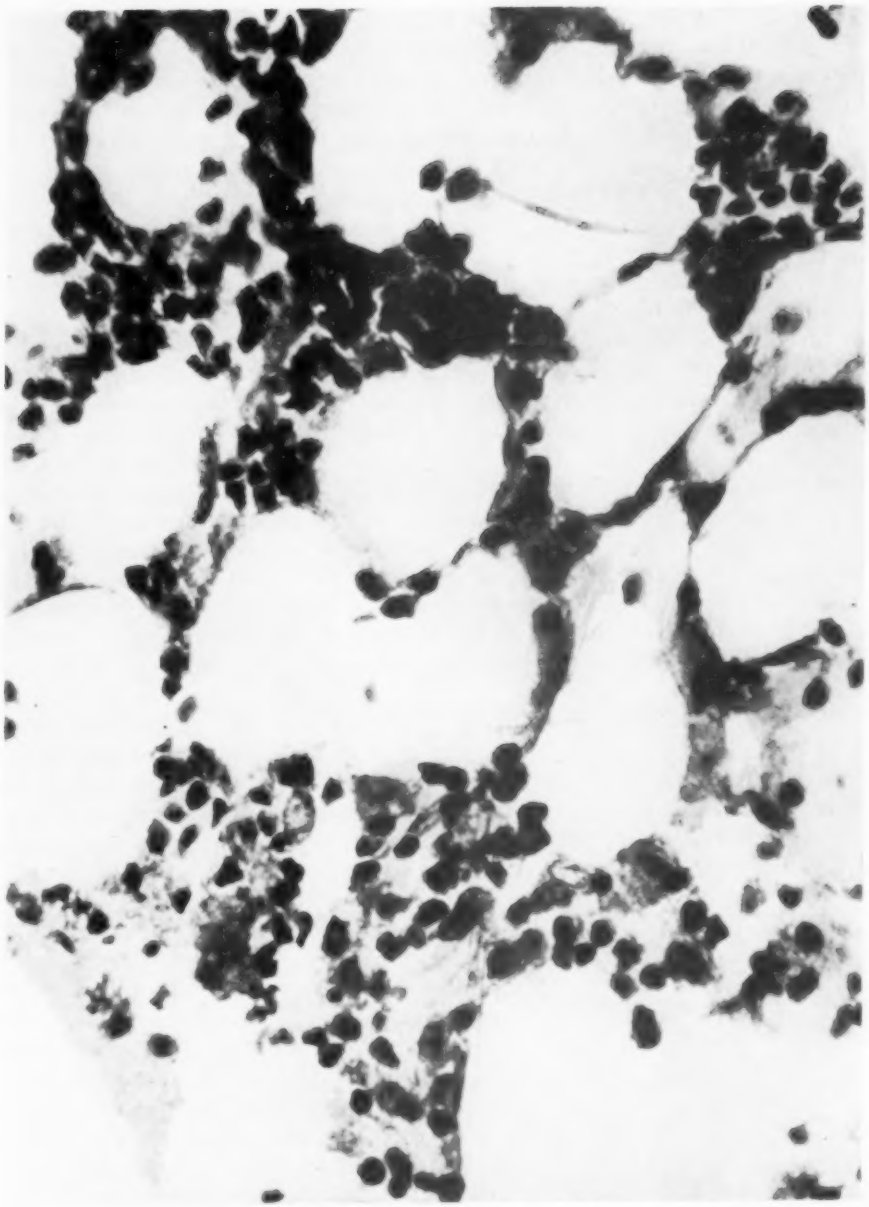

FIG. 1. Photomicrograph × 800 of Giemsa stain of rib marrow from the patient with aplastic anemia, obtained at necropsy. Note the aplasia with beginning islets of regeneration.

symptoms. In most of the reported cases of aplastic anemia from gold the symptoms have begun within one month of cessation of treatment. Many cases of "idiopathic" aplastic anemia have been recorded, but since the introduction of the sternal puncture method [5] of studying marrow, it has been learned that many cases with this blood picture are actually cases of aleukemic or subleukemic leukemia. In most of the patients with a truly aplastic marrow [6] a definite cause such as exposure to benzol, benzol ring drugs, gamma, alpha or beta radiation, can be found. Another rare cause of aplastic anemia is the end-stage of certain cases of lymphocytic leukemia.[7] The authors have recently seen a patient belonging to this group who was admitted to Multnomah County Hospital in August 1937, with enlargement of the spleen and lymph nodes, petechiae in the skin, and a sternal marrow showing a great increase in lymphocytes with many prolymphocytes and lymphoblasts. This patient refused treatment and left the hospital but returned in June 1938, a few hours before he died. A complete necropsy with careful examination revealed no evidence of leukemia, whatsoever, and typical aplastic marrow. The spleen was no longer enlarged, and it seems certain that had this patient been seen only on his last admission, he would have been classified as "idiopathic" aplastic anemia. Lymphocytic leukemia with terminal aplasia can be excluded here because of the long period of observation before the onset of this patient's anemia. The combination of benzol ring drugs and low vitamin B_1 intake [8] can be excluded because her previous diet was high in vitamin content, and there was no history of administration of benzol ring drugs and no response to a high vitamin B_1 intake. It must be concluded that the etiology in this patient is not known although delayed absorption of gold salts from the oily suspension can not be excluded.

The transfusions were given daily for definite reasons. It has been shown [9] that in patients and animals with aplastic anemia due to benzol poisoning or excessive gamma ray exposure the marrow will eventually regenerate if they survive. From the clinical condition of the patient when first seen and the extreme depletion of the erythrocyte, granulocyte, and thrombocyte series in both the bone marrow and the blood, it seemed unlikely that she could live more than a few days without transfusions to supply all of these three types of cells essential for her survival. It has been shown [10] that neutrophile lobocytes live only about 48 to 90 hours, and the duration of life of the platelets is thought to be rather short. Since one transfusion represents only about one-tenth of the volume of the patient's blood, one could hope to increase the level of a particular cell type by only about one-tenth of the concentration in the donor's blood. It can readily be calculated from these data that transfusions to maintain life with relatively complete aplasia of the marrow must be given at frequent intervals. Since the duration of life of the akaryocytes has been variously estimated at from 30 [11] to 80 [12] days, it is evident that if enough transfusions are given to maintain a sufficient number of neutrophiles and platelets to sustain life, a polycythemia will ultimately develop, as occurred in this case. Splenomegaly with active phagocytosis and rapid destruction of akaryocytes developed in this patient, apparently as a compensatory mechanism. This simulated closely the pathology in the spleen and liver in polycythemia rubra vera and suggested that the changes in the spleen and liver in this disease may be purely secondary. The possibility of separating the platelets and leukocytes from the

akaryocytes by fractional centrifugation was considered. The danger of introducing infection by the extra manipulations out-weighed the advantages. Eventually, it is hoped that marrow culture technic [2] may lead to the development of pure cultures of cell types for use in these conditions. Bleeding as a method of controlling the polycythemia was decided on as a safer and simpler procedure.

Because of the relatively complete aplasia of the marrow and the relative freedom from hemorrhage, it seemed possible that the duration of life of the akaryocytes might be calculated from the data on the amounts of blood transfused and the counts at intervals, thereafter. However, counts were not made on the donor's bloods, and the errors in the measurement of the volume of blood transfused, in the estimation of the patient's blood volume, and in the estimation of the donor's blood counts on the basis of normals, are too numerous and cumulative to justify such calculations. The erythrocyte counts up to November 21 fit very well with the counts calculated on the basis of a duration of life of the akaryocytes of 40 days if it is assumed that 500 c.c. represents one-tenth of the patient's blood volume, and that the donors had an average akaryocyte count of 5.0 million. Studies with the technic of marrow culture [10] offer promise of a much more accurate solution of this problem.

There were several reasons for administering sternal marrow intravenously in the manner employed. It seemed possible that in complete aplasia of the marrow there might be no remaining cells from which new marrow could develop. Intrasternal injection of marrow had been tried by one of us (E. E. O.) in another patient with aplastic anemia, and it had been found to be impossible to inject, apparently because collapse of the sinuses acted as a valve preventing egress of blood to make space for the injected marrow. Even if intrasternal injection of marrow were successful, it seems doubtful whether an adequate blood supply to the central areas of the injected material would be developed before necrosis had occurred. It is known that a small number of immature cells of the marrow are present even in normal blood, and it seems possible that the development of hyperplastic marrow in areas of normally fatty marrow may normally occur by means of blood stream metastasis.

The chief danger of intravenous marrow injection was considered to be fat embolism. For that reason, the marrow was first mixed with a considerable volume of blood from the same donor, and then very thoroughly mixed, with the hope that some of the free fat would be held in solution or suspension by the usual mechanisms of blood plasma for carrying fat. The absence of any evidence of a reaction in this patient would indicate that this procedure was successful. The donor chosen was a relative and of the same blood group (A) with the thought that such marrow might be more likely to survive than marrow from another donor. There is no evidence in this case that the marrow injection was effective. It apparently did no harm. It is possible that the regenerating islets in the marrow at the time of death were developed from the injected marrow cells, but there is no way of proving this. Certainly, the immature cells disappeared from the blood quickly. No foci of hematopoiesis were found outside of the marrow at necropsy. However, this could have been accounted for by destruction of the cells as well as by their localization in the marrow.

In this patient the injection of marrow was delayed until all hope from

other methods of therapy seemed gone because it was a new procedure. It would seem justifiable to try this method of therapy earlier next time in view of the seriousness of the disease, the logic underlying the therapy, and the absence of untoward reactions in this patient.

The extreme susceptibility of patients with aplastic anemia to infection is well known. This case illustrates the importance of efforts to guard these patients from every possible source of infection. Sodium perborate was used locally in the mouth, and transfusions were given to combat infection of the mucous membranes which commonly develops when the neutrophile lobocytes in the blood are markedly decreased in number. This infection which occurs in agranulocytosis and acute or subacute leukemia as well as in aplastic anemia appears to result from invasion by organisms already present in the mouth. In our experience, transfusions to provide the necessary number of granulocytes combined with sodium perborate to supply the additional peroxidase usually prevents such infections. Since the absolute neutrophile count only once exceeded 100 per cu.mm. after November 22, it seems likely that the perborate prevented stomatitis in this case.

It is noteworthy that the major drop in neutrophiles occurred from November 17 to November 21, in the period immediately following omission of five transfusions on November 14 to 18.

The abscess on the buttock would not have developed if no intramuscular preparations had been given. Neither pentose nucleotide nor liver extract had any apparent effect.

The acute streptococci follicular tonsillitis might have been prevented by isolation. Possibly this tonsillar infection was the source of the infection in the lungs, especially in view of the studies of Larsell, Veazie, and Fenton,[13] showing that infection from the sinuses and tonsils reaches the lungs by the route of the lymphatics and veins. This intravascular infection found at necropsy in the lungs undoubtedly explains the group of symptoms which were thought to be due to miliary tuberculosis, and accounts for the rapid downward course in the last week of life. It preceded the injection of sternal marrow so could hardly have been due to infected fat emboli. It also seems possible that she might have recovered had not this infection supervened in view of the beginning regeneration in the marrow and her relatively good condition until the onset of this infection.

The terminal bronchopneumonia, while probably the immediate cause of death, was similar to that which occurs in any patient who is moribund from any cause.

A number of lessons may be drawn from this case. Transfusions may be necessary daily or oftener in patients with complete aplasia of the bone marrow. In such patients omission of transfusion before marrow regeneration is well advanced may be disastrous. The frequency of transfusion depends on the necessities of each patient. Earlier intravenous injection of sternal marrow deserves further experimental trial. Patients with this disease should be carefully protected from every source of infection.

Summary

A patient with aplastic anemia lived 53 days after admission to the hospital in extremis. She died as a result of intercurrent infection. She received

43 transfusions, totalling 21,870 c.c. of blood within a period of 52 days. So far as we can determine, this is the largest amount of blood ever transfused into one person in this period of time. Sternal marrow was administered intravenously without untoward reaction.

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EDITORIAL

EQUINE ENCEPHALOMYELITIS IN MAN

The demonstration of the occurrence of equine encephalomyelitis in man adds another to the long list of human virus diseases. It also gives new interest and practical significance to some recent observations bearing on the epidemiology of this disease. It was first recognized by Meyer and his associates [1] in 1930 in a serious epizootic among horses in California. These observers isolated the virus from several animals in the earliest stages of the disease, and differentiated it from the other known viruses. They reproduced the disease in mice, rats, rabbits, monkeys, and most easily in guinea pigs, which were susceptible not only to intracerebral but also to intraperitoneal, intracutaneous and intranasal inoculation. They observed what they thought to be three cases of the disease in man but did not obtain direct proof of the presence of the virus in these cases.

In 1932 a similar disease was observed in horses in New England and the Atlantic states by Ten Broeck and Merrill [2] and others.[3] These workers isolated a virus which was serologically distinct from that which Meyers had obtained in California. This virus, which is designated as the Eastern type of equine encephalomyelitis, is even more virulent than the Western type, causing a mortality of about 90 per cent among the horses attacked.

In 1938 during an extensive epizootic of the Western type of infection among horses in Minnesota, Eklund and Blumstein [4] reported six cases of encephalitis with two deaths among farmers who had been in contact with diseased animals. One case which came to autopsy showed lesions in the central nervous system quite similar to those observed in animals. The virus was not isolated from any of these cases, but blood serum from one patient who recovered protected animals effectively from infection with the Western type of encephalomyelitis virus.

In 1938 another extensive outbreak of the Eastern type of encephalomyelitis occurred among horses in New England. Simultaneously cases of human encephalitis also appeared in the same localities. Feemster and his associates [5] made a study of 38 such cases, of which 25 were fatal. All but one were children and most of them were under ten years of age. The Eastern type of equine encephalomyelitis virus was recovered from the brain

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in eight cases by Fothergill et al.[6] and by Webster and Wright.[7] In seven other cases typical pathological lesions were found in the brain at autopsy. In four cases who recovered, a high degree of protective power for the Eastern type of virus was demonstrated in the blood. In one instance virus from a human source on intracerebral inoculation into horses produced the disease in one normal horse and in one immunized to the Western type of virus, whereas a horse immune to the Eastern type could not be infected.[8]

Quite recently Fothergill et al.[9] have reported a fatal accidental infection in a laboratory worker, from whom the Western type of virus was recovered.

The clinical course of the disease in man [5, 10] was characterized by a sudden onset with fever, irritability or drowsiness, often vomiting, headache and dizziness in older children, rigidity of the neck, cyanosis, muscular twitchings, convulsions and coma. Abnormalities of the reflexes were common but variable. Paralyses were occasionally observed. There was a polymorphonuclear leukocytosis. The cerebrospinal fluid was under increased pressure (200 to 350 mm. of fluid), was hazy, and showed from 200 to 2,000 cells per cu. mm. In the early stages from 60 per cent to 90 per cent of the cells were polymorphonuclear leukocytes, but in the later stages mononuclear cells predominated. The protein was much increased, the sugar usually normal.

Those who survived the acute stage often showed coma and muscular rigidity for a protracted period. Some patients who were thought to be cases of this infection recovered completely, others showed paralyses, mental disturbances or other permanent sequelae.

The brain in fatal cases, like that of experimental animals, showed edema and congestion, perivascular infiltration with leukocytes and plasma cells, some degree of cellular infiltration of the meninges, thrombi in the small vessels and focal areas of necrosis and infiltration.

These observations prove that man is susceptible to both the Eastern and Western types of the virus. The disease, at least in cases of obvious infection, runs a rapid course and has a high mortality. It differs clinically as well as serologically from the ordinary epidemic encephalitis, both of the Economo and St. Louis types.

The means by which the disease is spread are not known. In the case of the Massachusetts epidemic, contact with diseased animals could not be established. The incidence of the disease among horses does not favor the

[6] Fothergill, L. D., Dingle, J. H., Farber, S., and Connerly, M. L.: Human encephalitis caused by the virus of the eastern variety of equine encephalomyelitis, New England Jr. Med., 1938, ccxix, 411.

[7] Webster, L. T., and Wright, F. H.: Recovery of eastern equine encephalomyelitis virus from brain tissue of human cases of encephalitis in Massachusetts, Science, 1938, lxxxviii, 305.

[8] Schoening, H. W., Giltner, L. T., and Strahan, M. S.: Equine encephalomyelitis produced by inoculation of human encephalitis virus, Science, 1938, lxxxviii, 410.

[9] Fothergill, L. D., Holden, M., and Wyckoff, R. W. G.: Western equine encephalomyelitis in a laboratory worker, Jr. Am. Med. Assoc., 1939, cxiii, 206–207.

[10] Wesselhoeft, C., Smith, E. C., and Branch, C. F.: Human encephalitis. Eight fatal cases, with four due to the virus of equine encephalomyelitis, Jr. Am. Med. Assoc., 1938, cxi, 1735–1741.

theory of contact infection, and this has not been accomplished experimentally. The seasonal occurrence of the disease in horses during the summer and autumn with complete cessation during the winter suggested some biting insect as the vector. It was shown by Kelser [11] and later by Merrill and Ten Broeck [12] that the infection can be conveyed to guinea pigs by the bites of Aedes aegypti and of several other species of Aedes mosquitoes. The virus was found in the legs and body fluids of infected insects. However, no naturally infected mosquitoes have yet been found. The infection was not conveyed through the egg to the next generation, nor could it be transmitted to the female by the male. Furthermore the experimental transmission in their hands was difficult and uncertain unless the mosquito, after it had engorged, was injured by pricking the abdomen with a sharp needle. Transmission of the Eastern type of virus by biting was accomplished only once. It seems likely, therefore, that some other variety of arthropod is the usual vector.

There is considerable evidence also that the horse is not an important reservoir of the virus. The mortality among horses with clinical manifestations of the disease is very high (50 to 90 per cent), and the disease runs a rapid course. Furthermore the virus can be demonstrated in the blood only for a very brief period in the initial febrile stage of the infection before clinical symptoms are manifest. In a few cases virus has been recovered from the blood of horses naturally infected although no manifestations of illness other than fever ever appeared. A few horses have been found (about 15 per cent of those examined from infected areas), whose serum showed protective power although no previous illness had been recognized.[13] It is therefore possible for an animal to recover from the infection without developing encephalitis, but this appears to be uncommon. The possibility that the virus can maintain itself in horses seems remote.

As early as 1935 birds were suspected as being the reservoir host, partly because of the very wide range, yet sparse distribution of the disease along the Eastern coast.[13] Investigations both in Europe and America have shown that many different species of birds are susceptible to inoculation with the virus (pigeons, chickens, ducks, geese, storks, vultures, European blackbirds, barriers, etc.). Confirmatory evidence for this theory was furnished by Tyzzer, Sellards and Bennett [14] in 1938, who recovered the Eastern type of virus from the brains of four ring necked pheasants which were discovered paralyzed and moribund on a range in Connecticut. At about the same time Fothergill and Dingle [15] obtained the virus from the brain of

[11] Kelser, R. A.: Mosquitoes as vector of the virus of equine encephalomyelitis, Jr. Am. Vet. Med. Assoc., 1938, xcii, 195.

[12] Merrill, M. H., and Ten Broeck, C.: The transmission of equine encephalomyelitis by Aedes aegypti, Jr. Exper. Med., 1935, lxii, 687–695.

[13] Ten Broeck, C., Hurst, E. W., and Traub, E.: Epidemiology of equine encephalomyelitis in the eastern United States, Jr. Exper. Med., 1935, lxii, 677–685.

[14] Tyzzer, E. E., Sellards, A. W., and Bennett, B. L.: The occurrence in nature of "equine encephalomyelitis" in the ring-necked pheasant, Science, 1938, lxxxviii, 505–506.

[15] Fothergill, L. D., and Dingle, J. H.: A fatal disease of pigeons caused by the virus of the eastern variety of equine encephalomyelitis, Science, 1938, lxxxviii, 549–550.

a pigeon found dead in an infested area in New England. If the search for cases of spontaneous infection in migratory birds proves successful, as now seems probable, this will go far toward establishing this view that birds constitute the natural host for the virus. The horse and man appear to be merely accidental hosts, and are attacked only when conditions are especially favorable for the propagation of the infection. If this proves to be true, the term "equine" is obviously a misnomer.

Manifestly a great deal more work must be done before these problems are definitely solved. Enough is known, however, to indicate that the disease has become a serious public health problem, and that physicians should be alert to recognize the disease when it occurs.

P. W. C.

Erratum: In the article on "Visualization of the Chambers of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease; a Case Study," by Dr. George P. Robb and Dr. Israel Steinberg, the legend (except for the figure number) given for figure 6 (page 26) should appear with figure 7 (page 28); likewise the legend appearing under figure 7 should be with figure 6.

REVIEWS

Clinical Gastroenterology. By HORACE WENDELL SOPER, M.D. 314 pages; 25.5 × 17.5 cm. C. V. Mosby Co., St. Louis, Missouri. 1939. Price, $6.00.

Textbooks and monographs are often written in a very impersonal manner, and they may present facts in a way that makes uninteresting reading. This is not true of Dr. Soper's book. He has the ability to write medical literature that seems to be alive.

This volume is concerned primarily, as its title implies, with the clinical aspect of gastroenterology. It is in no sense a reference book but is essentially a record of the experiences of the author, and in the discussions, emphasis is placed on the methods that Dr. Soper has found to be most satisfactory. One may not agree entirely with all of his views, but this does not detract from the inherent usefulness of the book. There are placed at the end of each chapter numerous, well selected roentgenograms. These add greatly to a better understanding of the text.

It is a book to be used by anyone who would like to know how another individual would handle a certain problem in gastroenterology. Its value is primarily for the internist or to one who already has a fundamental knowledge of the subject. The details are not given which would be necessary for the book to be of value to the general practitioner. There are no vague statements; the author gets to his points quickly; and, as stated above, the book itself is very pleasant to read.

F. G. D.

Clinical Pathological Gynecology. By J. THORNWELL WITHERSPOON, B.S.; B.A. and M.A.; M.D. 400 pages; 24.5 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, $6.50.

In the author's own words this book is ". . . a presentation of organic gynecological pathology and its clinical application. . . ." Intentional omissions by the author include discussions of embryology, congenital anomalies, clinical methods of examination and diagnosis, obstetrical injuries, malpositions of the uterus, and operative technic. The author has arranged the material under the headings of anatomical locations rather than under the similarity of diseases.

There are 13 sections and a total of 27 chapters. There are 271 illustrations which are clear and in the main are of gross and microscopic preparations. A few of the more important references are listed following each gynecological disease. There is an adequate index.

After describing the clinical pathologic features of each condition the author discusses treatment. Such an order provides the reader with a clear correlation of clinical, pathologic, and therapeutic factors rarely found in texts.

The sections on the anterior pituitary gonadotropic hormone and the ovarian hormones are sound, clear, informative, and bring up to date the knowledge regarding these hormones. Most controversial subjects are purposely merely touched upon, but the author definitely states his belief that the three common gynecological conditions of hyperplasia of the endometrium, uterine fibroids, and endometriomas have their origin in excessive stimulation of the various tissues concerned by the ovarian follicular hormone. Also there is a chapter on the relationship between estrogenic and carcinogenic principles.

There is an interesting chapter on the differential diagnosis of irregular uterine hemorrhage. Radium therapy is discussed in some detail.

Since the book presents such a refreshing approach to the correlation of clinical and pathologic gynecology, and since it is the result of the author's wide experience, it will be of value especially to the student and the practitioner.

J. E. S.

Biographies of Child Development. By ARNOLD GESELL, Ph.D., M.D., CATHERINE S. AMATRUDA, M.D., BURTON M. CASTNER, Ph.D., and HELEN THOMPSON, Ph.D. 328 pages; 24 × 16.25 cm. Paul B. Hoeber, Inc., New York City. 1939. Price, $3.75.

Two sub-titles help describe this book. "The mental growth careers of eighty-four infants and children," and "A ten-year study from the Clinic of Child Development at Yale University."

In 1928 Dr. Gesell published *Infancy and Human Growth* in which he reported his mental-growth studies of 123 infants and discussed them from the standpoint of diagnosis and prognosis. Ten year follow-up studies are now reported on about 85 of these children.

These studies are discussed under a variety of headings. Cases are presented to illustrate normal, retarded and accelerated rates of mental growth. A great deal of valuable material is given to illustrate atypical growth complexes and the various factors that influence them. Thus cases are described to show the effect on mental growth of physical factors such as endocrine disturbances, birth injury and various infections involving the central nervous system. Other types of factors are also discussed, such as heredity, prematurity, reading disability and poor home environment. As sample illustrations of their findings, mental-growth studies of six children in one family show that heredity sometimes shows its effect in a bimodal distribution rather then a blend of two strains. Thus three of these children show normal mental-growth curves while three are definitely retarded. Another case illustrates an acceleration in mental-growth rate following removal from an orphanage and placement in a foster home.

The findings in this book are of particular interest to those professions dealing with children; pediatricians, educators, psychologists and social workers. The presentation is scientific in the strictest sense. There are no involved theories, nor does the reader have to wade through the strange jargons and terminologies characteristic of psychological schools of thought. The whole volume is readable, thought provoking and informative.

H. W. N.

The Medical Applications of the Short Wave Current. By WILLIAM BIERMAN, M.D. (Including a Discussion of Its Physical and Technical Aspects by MYRON M. SCHWARZSCHILD, M.A.). 379 pages; 23.5 × 16 cm. William Wood & Company, Baltimore. 1938. Price, $5.00.

The author is one of this country's prominent specialists in Physical Therapy and a book by him on this important subject is quite welcome at this time. The subject deals with a comparatively recently developed physical modality that is apparently the most effective means of applying heat to the body, especially to its deeper portions. The nomenclature is still unsettled and it seems to this reviewer unfortunate that Dr. Bierman follows the German terminology in the use of the term "short wave" which is an inadequate designation. The distinction between long and short waves might apply to various portions of the electromagnetic range, to roentgen-rays, to actinic rays, to heat rays. Why should one assume that the term "short wave" refers only to the region of high frequency electrical phenomena? The term "diathermy" has been in common use for many years and "short wave diathermy," a designation widely used in this country, seems an adequate one. High frequency electrotherapy is another term that is sufficiently definite.

One of the useful features of the book is the discussion of the physical and technical aspects in which a physicist endeavors to present these factors to the reader with no great store of physics in his memory. He begins with the simpler electrical concepts and proceeds step by step to the complicated high frequency field. The uninitiated physician will find his ideas to some extent clarified by a single reading of

this section and doubtless much more so by re-reading it once or twice. To those interested in the physics of the radio it will, of course, be child's play for the application of this method to medicine has after all been a fortunate by-product of the intense activity of physicists in the field of radio communication.

Following the section on Physics, there are chapters on "Temperature Determination in the Living Human," "Physiologic Responses to Local Heat and Local Short Wave Currents," and "Specificity," after which in Part II, are considered "Technique" and "Clinical Applications." Each system of the body is taken up in turn. The sections on physiology and on clinical applications are really reviews of the world literature with the author's experience and opinions concerning those features with which he himself has worked. There is an imposing bibliography at the end of the volume and a good index.

One might wish that this well qualified author had given a more critical presentation of the clinical literature but he disclaims any such intention. He states, "We have attempted to indicate therapeutic evaluations based on our own clinical experiences as correctly as our limitations will permit. In the desire to make as wide reference as possible to the therapeutic experiences of others, we are noting them for the reader's information without attempting to evaluate their accuracy, and even though the assertions appear to us to be far-fetched."

T. P. S.

Behandlung rheumatischer Erkrankungen mit Ultra-Kurzwellen. By PROFESSOR DR. ERWIN SCHLIEPHAKE (Mit 27 Abbildungen). 105 pages; 22 × 14.5 cm. Theodore Steinkopff, Dresden and Leipzig. 1938.

Schliephake's name is more widely known than any other in the field of short wave diathermy. At about the same time the method was being developed in this country for the production of artificial fever, Schliephake in Germany, in 1929, was the first to use this electrical means for the treatment of local disease, and he has written voluminously concerning its use since that time. He is enthusiastic in regard to its possibilities and is an exponent of the idea that the electrical phenomena have some specific effect on the tissues and functions of the living body and are not effective merely by reason of the heat induced. Similarly he is inclined to attribute varying effects to different wave lengths.

There is little, however, concerning such theories in this small volume which is one of a series on "Rheumatism," edited by Professor Rudolf Jürgens. The author presents his views on the nature and etiological factors of rheumatic diseases and discusses the technic and results of treatment by means of ultra short wave diathermy. He makes use of wave lengths of 3 and 3½ meters, definitely shorter wave lengths (or higher frequency), than those available commercially in this country. Wave lengths below 6 meters are spoken of as ultra short waves.

Not only does this European author accept the doctrine of focal infections as a most important concept in the etiology and treatment of rheumatic diseases but he treats these foci of infection as well, with his ultra short waves. Furthermore he quotes and accepts Gutzeit and Küchlin's work to the effect that a treatment of a suspected dental granuloma by means of short wave diathermy will cause an increase in the sedimentation rate of the red blood cells if this granuloma is active as a focus of infection and hence gives valuable information as to whether or not this focus should be eradicated.

The author has had an extensive experience and the opinions expressed concerning his results in the treatment of infected foci and of the joints in different types of arthritis seem reasonably conservative. It is, however, a little disconcerting to have him state, as he does several times, that he not infrequently sees a favorably result of therapy appear as long as 6 or 8 weeks after the cessation of the treatment.

T. P. S.

COLLEGE NEWS NOTES

New Life Member

Dr. C. D. Mercer, F.A.C.P., West Union, Iowa, became a Life Member of the American College of Physicians on July 29, 1939.

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Reprints

Dr. Benjamin M. Bernstein (Associate), Brooklyn, N. Y.—7 reprints;
Dr. Charles A. Bohnengel (Associate), New York, N. Y.—1 reprint;
Dr. William W. Cadbury, F.A.C.P., Canton, China—1 reprint;
Dr. H. M. Cleckley (Associate), Augusta, Ga.—1 reprint;
Dr. G. Philip Grabfield, F.A.C.P., Boston, Mass.—6 reprints;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—7th, Second Series, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";
Dr. Ben R. Heninger, F.A.C.P., New Orleans, La.—5 reprints;
Dr. William G. Herrman, F.A.C.P., Asbury Park, N. J.—2 reprints;
Dr. L. Dale Huffman, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. James H. Hutton, F.A.C.P., Chicago, Ill.—2 reprints;
Lt. Col. John G. Knauer, F.A.C.P., Denver, Colo.—1 reprint;
Dr. Sidney F. LeBauer (Associate), Greensboro, N. C.—1 reprint;
Dr. D. O. N. Lindberg, F.A.C.P., Decatur, Ill.—1 reprint;
Dr. Henry A. Monat (Associate), Washington, D. C.—3 reprints;
Dr. Samuel E. Munson, F.A.C.P., Springfield, Ill.—1 reprint;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—4 reprints;
Dr. Albert E. Russell, F.A.C.P., Chicago, Ill.—1 reprint;
Dr. Paul F. Stookey, F.A.C.P., Kansas City, Mo.—1 reprint;
Dr. Herman Tarnower (Associate), Scarsdale, N. Y.—1 reprint;
Dr. Stuart L. Vaughan (Associate), Buffalo, N. Y.—1 reprint;
Dr. August A. Werner, F.A.C.P., St. Louis, Mo.—1 reprint.

Dr. James G. Carr, F.A.C.P., College Governor for Northern Illinois, was elected President of the Chicago Society of Internal Medicine at its last annual meeting. Dr. LeRoy H. Sloan, F.A.C.P., was elected Vice-President.

Captain Frederick Ceres, F.A.C.P., has been appointed Medical Officer in command of the Medical Department of the U. S. Naval Air Station, Pensacola, Fla., this station being reputed to be the largest naval air station in the world.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, on July 27, 1939 was awarded the honorary degree of Master of Arts in Medicine by the Hahnemann Medical College of Philadelphia, with the following citation:

"For his ability as a Health Officer as manifested by the outstanding merit credited to the Department of Public Health of San Francisco; for his research in public health problems, especially in the fields of food poisoning, epidemiology and communicable disease; for his inspiration and instruction as a teacher of the medical student and public health worker; for his high degree of integrity, tenacity of purpose and devotion to duty and public welfare, and the recognition of his personal characteristics of the true Southern Gentleman; for his love of home and family; for his contributions to science; and finally for his untiring and painstaking efforts in the practice of medicine in all its best aspects:—

"There is conferred upon Jacob Casson Geiger the honorary degree of Master of Arts in Medicine with all the rights and privileges appertaining thereto."

Dr. M. S. Rednick (Associate), Ossining, N. Y., addressed the Alumni of Lincoln Hospital, New York City, recently on "A Pathological Study of the Significance of the Systolic Murmur."

The Jefferson County (Alabama) Medical Society gave an informal subscription dinner, July 7, 1939, in Birmingham, for the presentation of citations for contributions to medicine beneficial to mankind, to Dr. Seale Harris, Sr., F.A.C.P., of Birmingham, and Dr. Tom D. Spies (Phillips Medallist of the A.C.P.), of Cincinnati. The Citation scroll was presented to Dr. Harris by Dr. M. S. Davie of Dothan, President of the Medical Association of the State of Alabama. The Citation scroll was presented to Dr. Spies by Dr. M. Y. Dabney, of Birmingham, Member of the State Board of Censors.

Dr. Solomon Solis-Cohen, F.A.C.P., Philadelphia, received the honorary degree of Doctor of Science (honoris causa) at the June, 1939, commencement of the Philadelphia College of Pharmacy and Science.

Dr. James Harvey Black, F.A.C.P., Dallas, has been elected president of the newly organized Texas Allergy Association.

Dr. Leslie M. Smith (Associate), El Paso, has been elected president of the Texas Dermatological Society for the current year.

Dr. Walter L. Treadway, F.A.C.P., formerly in charge of the U. S. Narcotic Farm at Lexington, Ky., has been assigned to the University of California Medical School, San Francisco, to direct a survey of the care of mental patients in the state.

Dr. Jacob J. Singer, F.A.C.P., Los Angeles, is director of the Rose Lampert Graff Foundation at the Cedars of Lebanon Hospital, Los Angeles, for the study of respiratory diseases. $10,000 have been donated by Mr. and Mrs. Ellis Levy, Beverly Hills, for 1939, and plans are being considered to continue it for five years.

Dr. Charles H. Neilson, F.A.C.P., St. Louis, and Dr. E. Sanborn Smith, F.A.C.P., Kirksville, were recently appointed to the Missouri State Board of Health.

Dr. Eugene M. Landis, F.A.C.P., in 1936 Phillips Medallist of the American College of Physicians, assistant professor of medicine at the University of Pennsyl-

vania School of Medicine, has accepted the appointment as professor of internal medicine at the University of Virginia Department of Medicine, to succeed the late Dr. James C. Flippin.

Dr. Henry W. F. Woltman, F.A.C.P., Rochester, Minn., is a vice-president of the American Neurological Association for the current year.

Dr. Dudley W. Bennett, F.A.C.P., has been promoted to associate clinical professor of medicine at the University of California Medical School, San Francisco.

Dr. Edward J. Murray, F.A.C.P., Lexington, has been elected President of the Kentucky Hospital Association.

Dr. William Halsey Barker (Associate), instructor in medicine at Johns Hopkins University School of Medicine, Baltimore, has been appointed assistant dean. Dr. Barker will assist the dean in the field of student relations and will serve as a member of the committee on admissions to the medical school.

Dr. Guy W. Wells, F.A.C.P., Providence, is secretary of the Rhode Island Medical Society for the current year.

Dr. William H. Kelley (Associate) has been advanced to professor of medicine at the Medical College of the State of South Carolina, Charleston.

Dr. Hugh J. Morgan, F.A.C.P., professor of medicine at Vanderbilt University School of Medicine, Nashville, is one of those appointed recently by Governor Cooper to the "Advisory Board of Medical Care of State's Wards," to make a thorough study of the state's institutions and to recommend improvements in the present system of medical care for the inmates.

Major General Charles R. Reynolds, F.A.C.P., U. S. Army (Retired), has been elected president of the Association of Military Surgeons of the United States.

Dr. William E. Costolow, F.A.C.P., Los Angeles, is secretary of the American Radium Society.

Dr. Harold W. Gregg, F.A.C.P., Butte, has been installed as President of the Medical Association of Montana.

The advisory council on postgraduate medicine of the Wayne County Medical Society, Detroit, has determined upon an extension of its postgraduate program, and has elected officers including a secretary, executive secretary, and Dr. William J. Stapleton, Jr., F.A.C.P., as registrar. "The continuation school of medicine of Wayne County" will offer courses in the specialties to general practitioners, utilizing facilities of the county medical society, Wayne University College of Medicine, local hospitals, the Department of Welfare, and the Detroit Department of Health. It is proposed to start courses in the autumn with bedside teaching of general medicine, groups being limited to from four to six physicians. Other courses will be added as the program progresses.

The Seventh Annual Assembly of the Omaha Mid-West Clinical Society will be held at Omaha, October 23–27, 1939. Among distinguished guests presenting addresses and clinics are the following:

Medicine

Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill.
Dr. William R. Houston, F.A.C.P., Austin, Tex.
Dr. Samuel A. Levine, F.A.C.P., Boston, Mass.

RECENT ANNOUNCEMENTS

American Board of Internal Medicine Examinations

The next written examination by the American Board of Internal Medicine is scheduled for October 16, 1939, to be given in various centers. For specific information address the Secretary-Treasurer, Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

Advisory Council on Medical Education

The Advisory Council on Medical Education has been organized with the following Officers and Executive Committee:

Officers

Dr. Willard C. Rappleye, F.A.C.P., Dean of the Faculty of Medicine of Columbia University ..... President
Dr. Maurice H. Rees, Dean of the School of Medicine of the University of Colorado ..... Vice-President
Dr. Robin C. Buerki, Director of Study of the Commission on Graduate Medical Education .....Secretary-Treasurer

Executive Committee, Including the Above Officers and the Following:

Dr. Anton J. Carlson, F.A.C.P., Professor of Physiology of the University of Chicago
Dr. Harold Rypins, F.A.C.P., Secretary of the New York State Board of Medical Examiners
Dr. Hugh J. Morgan, F.A.C.P., Professor of Medicine of Vanderbilt University
Dr. Arthur W. Allen, Surgeon, Boston

The organizations represented on the Advisory Council are as follows:

American College of Physicians—2 representatives;
American College of Surgeons—2 representatives;
Association of American Medical Colleges—3 representatives;
American Hospital Association—3 representatives;
Catholic Hospital Association—1 representative;
Federation of State Medical Boards of the United States of America—3 representatives;
Advisory Board for Medical Specialties—3 representatives;
National Board of Medical Examiners—1 representative;
Association of American Universities—2 representatives;
American Public Health Association—1 representative;
American Association for the Advancement of Science, Division of Medical Sciences—1 representative;
American Protestant Hospital Association—1 representative;
Association of American Colleges—2 representatives.

Successor to Late Dr. Alfred Stengel Announced

Dr. Alfred Newton Richards, Professor of Pharmacology in the University of Pennsylvania School of Medicine, has been elected Vice-President of the University in charge of Medical Affairs to succeed the late Dr. Alfred Stengel. The selection of Dr. Richards, whose researches upon the mechanism of kidney function have won for him world wide acclaim, is a fortunate one for the University because he is in a position to strengthen and integrate research, teaching, and the practice of medicine. The successful performance of this function is vital to an institution where interest lies not only in the care of the sick, but also in a search for the cause and cure of disease. Through his own long experience in research both here and abroad Dr. Richards is eminently qualified for this task.

In recognition of his distinguished achievements in the field of medical research, Dr. Richards has been awarded the Kober Medal of the Association of American Physicians, the Gold Medal of the Academy of Medicine of New York, and the William Wood Gerhard Medal of the Philadelphia Pathological Society. In 1938 he was presented with the Philadelphia Award, which was endowed in 1921 by the late Edward W. Bok and is conferred annually in recognition of outstanding service to the community of which this city is a part. Dr. Richards has received honorary degrees from the University of Pennsylvania, Yale University, Western Reserve University, and the University of Edinburgh, Scotland.

Association of Military Surgeons of the United States

The Henry Wellcome Medal

The Wellcome Gold Medal and cash prize of $500 awarded annually by the Association of Military Surgeons of the United States, was established in 1916 by the late Sir Henry Wellcome with the endorsement of the Council of the Association.

The Gold Medal, which was designed by Sir Henry Wellcome, bears on the reverse a representation of the seal of the Association of Military Surgeons of the United States. On the obverse are the heads of Machaon and Polaleirios, Homer's "two famed surgeons" of the Greek army in the Trojan War.

The Medal together with the cash prize is awarded annually "for researches, discoveries, inventions, designs, improvements, essays, or any other acts or deeds which the Executive Council of the Association may consider desirable and helpful to the objects of the Association, and relating to any phase of medico-military affairs and disease control associated with the Army, Navy, Militia and Public Health and Marine Hospital Service in times of peace or war at home or abroad."

Announcement of the annual competition is published each year in the official organ of the Association, "The Military Surgeon." The award is made for the best paper on the subject assigned each year in the published announcement. Additional particulars may be obtained by addressing the Secretary of the Association of Military Surgeons of the United States, Army Medical Museum, Washington, D. C. A replica of the Medal and an interesting history of its design have been presented to the American College of Physicians.

Institute for the Consideration of the Blood and Blood-Forming Organs

The University of Wisconsin Medical School will conduct an Institute for the Consideration of the Blood and Blood-Forming Organs, September 4–6, 1939, at Madison. The Wisconsin Alumni Research Foundation has made available the

necessary funds to finance this Institute. Among Fellows of the American College of Physicians who will participate on the program appear the following:

Dr. Charles A. Doan, Professor of Medicine at the Ohio State University, Leader of the Round Table on "The Etiology and Therapy of Granulocytopenia," an assistant to the leader in the Round Table on "Consideration of Some of the Diseases Affecting Lymph Nodes," and to deliver a paper on "The Reticulo-Endothelial System";

Dr. George R. Minot, Professor of Medicine and Director of the Thorndike Laboratory, Harvard Medical School, Leader of the Round Tables on "Etiologic and Therapeutic Aspects of the Hemorrhagic Diseases" and "Therapy of the Anemias," and to deliver a paper on "Anemias of Nutritional Deficiency";

Dr. Russell L. Haden, Chief of the Medical Division, Cleveland Clinic, to deliver a paper on "The Nature of the Hemolytic Anemias," and to act as a Leader of the Round Table on "Therapy of the Anemias";

Dr. Claude E. Forkner, Assistant Professor of Clinical Medicine, Cornell University Medical College, to deliver a paper on "Monocytic Leukemia and Aleukocythemic Leukemia" and to assist the Leader in a Round Table on "The Treatment of Leukemia";

Dr. E. B. Krumbhaar, Professor of Pathology at the University of Pennsylvania School of Medicine, to deliver a paper on "Hodgkin's Disease" and to lead a Round Table on "Consideration of Some of the Diseases Affecting Lymph Nodes."

American College of Physicians House Committee Solicits Suggestions

In the Board Room of the College Headquarters, 4200 Pine Street, Philadelphia, there is a wall space above the mantle, 43 inches broad and 36 inches high, which offers a splendid opportunity for an original painting or etching.

The Board Room is finished in oak paneling and the proposed painting will be the highlight of the room.

The House Committee desires suggestions from the membership at large in order that an appropriate and dignified work of art may be selected. One subject might represent some event in the development of medicine, preferably occurring in North America. Another possibility might be found in some historical event of importance in connection with the origin and growth of The College.

The House Committee will appreciate suggestions regarding the type and subject of the proposed picture. It will also be receptive to offers from any member who desires to underwrite same.

Communications should be addressed to the Chairman of the House Committee, Edward L. Bortz, M.D., 2021 W. Girard Avenue, Philadelphia, Pennsylvania.

OBITUARIES

DR. CHARLES ADDISON ELLIOTT

Charles Addison Elliott, Fellow of the American College of Physicians, died at the Passavant Memorial Hospital, Chicago, Illinois, on June 26, 1939, of cardiovascular disease.

Dr. Elliott was born in Lincoln, Nebraska, March 6, 1873. He received his degree of B.S. at the University of Nebraska in 1895 and in 1898 was graduated from Northwestern University Medical School. Following this, he served for a year and a half as an interne at the Mercy Hospital in Chicago. Later he studied at the University of Vienna and soon after began teaching at the Northwestern University Medical School. He continued in this department of Northwestern through the rest of his life, eventually attaining the position of Professor of Medicine, and for some twenty years serving as Chief of the Department of Medicine at the Northwestern University Medical School.

For many years, Dr. Elliott was a member of the staff of Wesley Memorial Hospital during a large part of which time he was the Chief of the Medical Staff. Since 1929 he was attending physician and Chief of the Medical Staff at the Passavant Memorial Hospital.

Dr. Elliott was a member of the Chicago Medical Society, the Illinois Medical Society and the American Medical Association. He served one year as Vice-President of the American Medical Association. He was a member of the Institute of Medicine of Chicago, which he also served as Vice-President for a term. He was a charter member of the Chicago Society of Internal Medicine, which he served as Secretary and as President. He was a member of the Association of American Physicians. He was active in the organization of the Central Society for Clinical Research. He was a member for many years of the Interurban Clinical Club of which he also served as Secretary and as President. He has been a Fellow of the American College of Physicians since 1929.

He published many articles in the current literature and was frequently called upon throughout the country for addresses on medical subjects.

Through many years Dr. Elliott has been regarded as one of the outstanding members of the medical profession in Chicago particularly in his chosen line of work—internal medicine. He had a wide practice as a consultant and was highly regarded by the profession. Practically from the time of his interneship he was engaged in teaching. He was especially interested in his work at the Medical School and will be long remembered by hundreds of his students for his enthusiasm, his knowledge of medicine and his unusual capacity for teaching.

The profession in Chicago and throughout the country has lost a man of unusually attractive personality and character. Dr. Elliott will be especially mourned by those with whom he worked, his students, his associates in the Medical School, and the various societies of which he was a

member, by all those who were most closely associated with him. His interest in medicine and his skill in medicine combined with an unusual ability to teach were of service to students for many years. Yet, the greatest impression that Dr. Elliott made upon those who knew him was that of his own honesty, kindness, thoroughness and devotion to his patients; these things, he taught by example.

Dr. Elliott leaves a widow and three children. A son and daughter are both students in Northwestern University Medical School.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

DR. SAMUEL CALVIN SMITH

Dr. Samuel Calvin Smith of Philadelphia, a Fellow of the American College of Physicians since April 5, 1923, died July 31, 1939, in the General Hospital, East Stroudsburg, from injuries suffered in an automobile accident.

Dr. Smith was born in Hollidaysburg, Pennsylvania, February 28, 1881, and was educated there and at Bucknell University, from which he was graduated in 1901. After receiving his medical degree from Jefferson Medical College of Philadelphia, he returned to his native city to practice until 1916.

During the World War, Dr. Smith served as a major in the Army Medical Corps in France. He later became Instructor in medicine at Jefferson, which position he held from 1920 to 1922, and remained in Philadelphia to practice. He was consulting cardiologist from 1925 to 1930 at the Misericordia Hospital and West Chester Hospital and during 1931–32 at the Veterans' Hospital, Coatesville.

In addition to being a Fellow of the American College of Physicians, Dr. Smith belonged to the American Medical Association, and was a member of its special committee for the presentation of modern methods of heart study.

The passing of Dr. Smith leaves a large circle of friends who will greatly miss this eminent physician.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

DR. PHILIPS J. EDSON

Dr. Philips J. Edson, F.A.C.P., died on July 6, 1939, from coronary sclerosis, at his home in San Marino, California. Dr. Edson was born November 27, 1896, at Los Angeles. He attended the Manual Arts High School, received his A.B. degree in 1920, his M.A. degree in 1921 and his M.D. degree in 1924 from the University of California. He was an Assistant in Physiology at the University of California while working for

his M.A. degree; he interned at the Peter Bent Brigham Hospital in Boston from 1923 to 1925, and began practice in Pasadena in 1926; for a number of years he was Instructor in Medicine at the College of Medical Evangelists, Physician to the Los Angeles County Hospital and Senior Visiting Physician and Vice Chairman of the Medical Staff to the Huntington Memorial Hospital of Pasadena. He was particularly interested in internal Medicine and Cardiology.

Dr. Edson was a member of the Los Angeles County Medical Association, California State Medical Association, Los Angeles Clinical and Pathological Society, American Medical Association, California Heart Association, and had been a Fellow of the American College of Physicians since 1938. He was a member of Pasadena's University and Valley Hunt Clubs and the Rotary Club, and was well known and well liked by both his conferees and a wide circle of friends and acquaintances. He was a good physician who will be much missed by his friends and a sorrowing family.

EGERTON L. CRISPIN, F.A.C.P.,
Regent.

DR. MARY PRIESTLEY SHERIFF RUPERT

Dr. Mary Priestley Sheriff Rupert, F.A.C.P., of Bala-Cynwyd, Pennsylvania, a Fellow of The American College of Physicians since 1928, died July 21, 1939.

Dr. Rupert was born in Shamokin in 1880. She was graduated from the Woman's Medical College of Pennsylvania in 1904, and then interned at its hospital.

Dr. Rupert received postgraduate training at the University of Edinborough, Scotland, Johns Hopkins University School of Medicine, Harvard University Medical School and the New York Polyclinic Medical School.

Dr. Rupert was responsible for organizing the laboratory of clinical pathology at the Woman's Medical College where she was Clinical Professor of Medicine. For the last two years she had served on the executive committee of the Board of Corporators. She was on the board as representative of the alumnae of the college. In recent years she retired from the active practice of medicine.

Dr. Rupert was a member of the American Medical Association, Philadelphia County Medical Society, Pennsylvania State Medical Society, The American College of Physicians, and the American Medical Women's Association.

Dr. Rupert leaves a large circle of friends and professional colleagues with whom she has been on the most intimate terms and by whom she will be greatly missed.

EDWARD L. BORTZ, M.D., F.A.C. P.,
Governor for Eastern Pennsylvania.

DR. CARROLL JULIAN ROBERTS

With the death of Dr. Carroll Julian Roberts on April 6, 1939, Buffalo lost one of its outstanding citizens and the medical profession a distinguished member.

Dr. Roberts was born in Buffalo, New York, June 9, 1880, and was graduated from the University of Buffalo School of Medicine in 1903. He continued study in Berlin—at the Friedrichain Krankenhaus and the Charité Krankenhaus.

In 1934 Dr. Roberts was in charge of medical teaching at the Buffalo City Hospital with the rank of Professor of Medicine; Assistant Attending Physician at the Buffalo General Hospital; Director of the Peripheral Vascular Clinic at the Buffalo General Hospital and Consulting Physician at the J. N. Adam Memorial Hospital at Perrysburg.

He was a member of the Academy of Medicine, Erie County Medical Society, Medical Union, American Medical Association and a Fellow of the American College of Physicians since 1931. He served as Chairman of the Health Board, which post he resigned to accept the position of Clinical Director of the Buffalo City Hospital.

Dr. Roberts was a consistent, conscientious student and a splendid teacher. He had a wonderful personality and, in every way, showed himself to be a high type of medical teacher and practitioner.

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,
Governor for Western New York.